**No. 17-1480**

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**UNITED STATES COURT OF APPEALS**
**FOR THE FEDERAL CIRCUIT**

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AMGEN INC., AMGEN MANUFACTURING, LTD., and AMGEN USA, INC.,

*Plaintiffs-Appellees,*

v.

SANOFI, AVENTISUB LLC, REGENERON PHARMACEUTICALS INC., and SANOFI-AVENTIS U.S. LLC,

*Defendants-Appellants.*

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On Appeal from the United States District Court for the District of Delaware,
No. 14-1317-SLR (Consolidated), Judge Sue L. Robinson

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**CORRECTED BRIEF FOR DEFENDANTS-APPELLANTS**

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March 3, 2017

## CERTIFICATE OF INTEREST

Counsel for Appellants certifies the following:

**1. The full name of every party represented by us is:**

Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc.

**2. The name of the real party in interest represented by us is:**

Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc.

**3. All parent corporations and any other publicly held companies that own 10 percent or more of the stock of the party represented by me are:**

Sanofi has no parent corporation, and no publicly held company owns 10 percent or more of its stock. Sanofi is the parent corporation of sanofi-aventis and Aventisub LLC. Regeneron Pharmaceuticals, Inc. has no parent corporation. Sanofi, through Sanofi's directly and indirectly owned subsidiaries, owns 10 percent or more of Regeneron's stock.

**4. The names of all law firms and the partners or associates that appeared for Appellants in trial court or are expected to appear in this court are:**

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# TABLE OF CONTENTS

CERTIFICATE OF INTEREST ..... i

TABLE OF AUTHORITIES ..... vi

STATEMENT OF RELATED CASES ..... xi

JURISDICTIONAL STATEMENT ..... 1

STATEMENT OF THE ISSUES ..... 1

INTRODUCTION ..... 2

STATEMENT OF THE CASE ..... 5

A. Factual Background ..... 5

1. Appellants' Praluent ..... 7

2. Amgen's Repatha ..... 8

B. The Patents-in-Suit ..... 9

C. Procedural History ..... 11

1. Pretrial Proceedings ..... 11

a. Exclusion of Post-Priority-Date Evidence ..... 12

b. Exclusion of Prior Art References ..... 13

2. Trial Proceedings ..... 14

a. Written Description and Enablement ..... 14

b. Obviousness ..... 17

c. Jury Instructions ..... 18

3. Verdict, Post-Trial Motions, and the Permanent Injunction ..... 19

SUMMARY OF ARGUMENT ..... 20

STANDARDS OF REVIEW ..... 23

ARGUMENT ..... 24

I. The District Court's Exclusion Of Post-Priority-Date Evidence, Including Praluent And Other Antibodies Within Amgen's Functionally Claimed Genus, Was Prejudicial Error And Requires A New Trial On Written Description And Enablement. .............................. 24

A. A New Trial Is Required on Written Description. ............................. 24

B. A New Trial Is Required on Enablement. ......................................... 33

II. The District Court's "Newly Characterized Antigen" Instruction Requires A New Trial On Written Description. ........................................... 34

A. The "Newly Characterized Antigen" Instruction Has No Basis in the Patent Statute, Science, this Court's Precedent, or Common Sense. ....................................................................... 35

B. At a Minimum, the District Court's Version of the "Newly Characterized Antigen" Instruction Was Legally Deficient. ............. 41

C. In the Alternative, There Was Insufficient Evidence to Support the Jury Verdict Under the District Court's Instruction. ......................................................................................... 43

III. The District Court's Erroneous Grant Of JMOL Requires A New Trial On Obviousness. ........................................................................ 45

A. The District Court Improperly Extended *Drinkware* to Published Patent Applications. ........................................................ 46

B. Even if *Drinkware* Applied to Published Patent Applications, JMOL Was Improper. ...................................................................... 49

IV. In The Alternative, Appellants Are Entitled To Judgment As A Matter Of Law On Written Description Or Enablement. ............................ 52

A. Amgen's Written Description Is Insufficient as a Matter of Law. ............................................................................................... 54

B. Amgen's Claims Are Invalid as a Matter of Law for Lack of Enablement. ........................................................................................ 57

V. At A Minimum, The Permanent Injunction Order Should Be Vacated. ................................................................................................ 58

A. Granting an Injunction that Disserves the Public Interest Is Irreconcilable with *eBay* and Basic Principles of Equity. .................. 59

B. The Injunction Order Is Impermissibly Unreasoned.......................... 61

C. Ordering an Injunction Was an Abuse of Discretion.......................... 62

CONCLUSION .......................................................................................... 65

CERTIFICATE OF COMPLIANCE

ADDENDUM

CERTIFICATE OF SERVICE

## TABLE OF AUTHORITIES

### Cases

*Abbott GMBH & Co., KG v. Centocor Ortho Biotech, Inc.*,
870 F. Supp. 2d 206 (D. Mass. 2012) ....................30

*AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*,
759 F.3d 1285 (Fed. Cir. 2014) .................... *passim*

*ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*,
694 F.3d 1312 (Fed. Cir. 2012) ....................61

*Acumed LLC v. Stryker Corp.*,
551 F.3d 1323 (Fed. Cir. 2008) ....................24

*Amazon.com, Inc. v. Barnesandnoble.com, Inc.*,
239 F.3d 1343 (Fed. Cir. 2001) ....................29

*Amgen Inc. v. Hoechst Marion Roussel, Inc.*,
314 F.3d 1313 (Fed. Cir. 2003) .................... 50, 51

*Apple Inc. v. Samsung Elecs. Co.*,
809 F.3d 633 (Fed. Cir. 2015) ....................61

*Ariad Pharms., Inc. v. Eli Lilly & Co.*,
98 F.3d 1336 (Fed. Cir. 2010) .................... *passim*

*Ariosa Diagnostics, Inc. v. Illumina, Inc.*,
IPR2014-01093, 2016 WL 354412 (PTAB Jan. 7, 2016) ....................46

*Brown v. 3M*,
265 F.3d 1349 (Fed. Cir. 2001) ....................27

*Callaway Golf Co. v. Acushnet Co.*,
576 F.3d 1331 (Fed. Cir. 2009) ....................23

*Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*,
807 F.3d 1283 (Fed. Cir. 2015) ....................23

*Centocor Ortho Biotech, Inc. v. Abbott Labs.*,
636 F.3d 1341 (Fed. Cir. 2011) .................... *passim*

*Chiron Corp. v. Genentech, Inc.*,
363 F.3d 1247 (Fed. Cir. 2004) .......... 31, 32, 51

*Cordis Corp. v. Boston Sci. Corp.*,
99 F. App'x 928 (Fed. Cir. 2004) .......... 61

*Dynamic Drinkware, LLC v. National Graphics, Inc.*,
800 F.3d 1375 (Fed. Cir. 2015) .......... 13, 46, 47

*eBay Inc. v. MercExchange L.L.C.*,
547 U.S. 388 (2006) .......... 4, 59, 60

*Eli Lilly & Co. v. Barr Labs., Inc.*,
251 F.3d 955 (Fed. Cir. 2001) .......... 49

*Enzo Biochem, Inc. v. Gen-Probe Inc.*,
323 F.3d 956 (Fed. Cir. 2002) .......... 37, 38

*Ericsson, Inc. v. D-Link Sys., Inc.*,
773 F.3d 1201 (Fed. Cir. 2014) .......... 35

*Ex parte Robbins*,
No. 2009-001866, 2009 WL 3490271 (BPAI Oct. 27, 2009) .......... 48

*Ex parte Yamaguchi*,
88 U.S.P.Q.2d 1606, 2008 WL 4233306 (BPAI 2008) .......... 48

*Felkner v. Jackson*,
562 U.S. 594 (2011) .......... 62

*Fiers v. Revel*,
984 F.2d 1164 (Fed. Cir. 1993) .......... 28

*Fujifilm Corp. v. Benun*,
605 F.3d 1366 (Fed. Cir. 2010) .......... 23

*Genentech, Inc. v. Novo Nordisk A/S*,
108 F.3d 1361 (Fed. Cir. 1997) .......... 33, 57

*Hecht Co. v. Bowles*,
321 U.S. 321 (1944) .......... 61

*Highmark Inc. v. Allcare Health Mgmt. Sys., Inc.*,
134 S. Ct. 1744 (2014)........................................................ 23, 24, 32

*In re Antor Media Corp.*,
689 F.3d 1282 (Fed. Cir. 2012)........................................................50

*In re Giacomini*,
612 F.3d 1380 (Fed. Cir. 2010)........................................................51

*In re Goodman*,
11 F.3d 1046 (Fed. Cir. 1993)........................................................32

*In re Hogan*,
559 F.2d 595 (C.C.P.A. 1977)........................................................ 13, 30, 31

*In re Klesper*,
397 F.2d 882 (C.C.P.A. 1968)........................................................52

*In re Wertheim*,
646 F.2d 527 (C.C.P.A. 1981)........................................................ 46, 47, 48

*In re Wright*,
999 F.2d 1557 (Fed. Cir. 1993)........................................................32

*Koninklijke Philips Elecs. N.V. v. Cardiac Sci. Operating Co.*,
590 F.3d 1326 (Fed. Cir. 2010)........................................................50

*McQueeney v. Wilmington Trust Co.*,
779 F.2d 916 (3d Cir. 1985)........................................................32

*Monsanto Co. v. Geertson Seed Farms*,
561 U.S. 139 (2010)........................................................59

*Noelle v. Lederman*,
355 F.3d 1343 (Fed. Cir. 2004)........................................................ 38, 39

*Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*,
424 F.3d 1347 (Fed. Cir. 2005)........................................................50

*O'Reilly v. Morse*,
56 U.S. 62 (1853)........................................................3

*Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.*,
315 F.3d 1335 (Fed. Cir. 2003)....................31

*Regents of the Univ. of Cal. v. Eli Lilly & Co.*,
119 F.3d 1559 (Fed. Cir. 1997)....................55

*Rothman v. Target Corp.*,
556 F.3d 1310 (Fed. Cir. 2009)....................24

*SEC v. Teo*,
746 F.3d 90 (3d Cir. 2014)....................35

*Univ. of Rochester v. G.D. Searle & Co.*,
358 F.3d 916 (Fed. Cir. 2004).................... 36, 37

*Winter v. NRDC*,
555 U.S. 7 (2008)....................61

*Wyeth & Cordis Corp. v. Abbott Labs.*,
720 F.3d 1380 (Fed. Cir. 2013)....................58

**Statutes**

21 U.S.C. §360ff....................7

35 U.S.C. §112.................... *passim*

35 U.S.C. §162....................36

Pub. L. No. 106-113, 113 Stat. 1501A-561 (1999)....................47

**Rule and Regulations**

Fed. R. Civ. P. 50(a)(1)....................52

37 C.F.R. §1.14(a)(1)(v)....................48

37 C.F.R. §1.215.................... 48, 51

PTO, *Examination Guidance and Training Materials*
(Archived 2008), http://bit.ly/2kLrTLa....................37

PTO, *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, "Written Description" Requirement*, 66 Fed. Reg. 1099 (Jan. 5, 2001) ....................38

**Other Authorities**

157 Cong. Rec. S1369 (daily ed. Mar. 8, 2011)....................48

Amicus Br. for Amgen Inc., *Ariad Pharms., Inc. v. Eli Lilly & Co.*, No. 2008-1248 (Fed. Cir. Nov. 19, 2009)....................28

Amicus Br. for Eli Lilly, *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, No. 2010-1144 (Fed. Cir. Mar. 15, 2010) ....................39

Matthew Herper, *Could Amgen's Patent Victory Be Bad For Medicine?*, Forbes (Jan. 6, 2017), http://bit.ly/2ioTTmR....................60

Paula K. Davis & Steven P. Caltrider, *Timing (of Invention) Is Everything*, 15 Fed. Cir. B.J. 39 (2005)....................40

Prof. Rachel Sachs, *Let's All Worry About the Effects of Patent Injunctions Against Drug Manufacturers*, Harvard Law Bill of Health Blog (Jan. 6, 2017), http://bit.ly/2jhLYYM .................... 60, 63

## STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, Defendants-Appellants Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively "Appellants"[1]) state that no appeal from the action below has arisen before this Court or any other appellate court.

On January 13, 2017, Appellants moved this Court for a stay of the permanent injunction pending appeal under Federal Rule of Appellate Procedure 8(a)(2) and for an expedited merits briefing schedule. DE14. Plaintiffs-Appellees Amgen Inc., Amgen Manufacturing, Ltd., and Amgen USA, Inc. ("Amgen") opposed the stay but supported expedited briefing. The Court (Prost, C.J.) entered an order expediting briefing on January 18, 2017. DE22. The Court (Dyk, J., with Bryson, Stoll, JJ.) granted a stay of the injunction pending appeal on February 8, 2017. DE59.

Appellants are aware of no case pending in this Court or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

[1] Regeneron and Sanofi (initially Aventis) have been full partners in developing the pharmaceutical at issue in this case. Appx2146-2259; Appx1189(347:12-21). Accordingly, for brevity, this brief refers to Regeneron and Sanofi as "Appellants." Regeneron and Sanofi did not jointly undertake every single activity that this brief attributes to "Appellants," but the few such instances are immaterial for purposes of this appeal.

## JURISDICTIONAL STATEMENT

The district court had jurisdiction pursuant to 28 U.S.C. §§1331 and 1338(a). The district court entered a final judgment on liability on January 3, 2017, Appx27, and a permanent injunction on January 5, 2017, Appx28-34. Appellants filed a timely notice of appeal on January 12, 2017. Appx2462-2463. This Court has jurisdiction under 28 U.S.C. §1295(a)(1).

## STATEMENT OF THE ISSUES

**I.** Whether a new trial on written description and enablement is required because the district court improperly excluded evidence critical to Appellants' written description and enablement defenses.

**II.** Whether a new trial on written description is required because the district court erroneously instructed the jury on the written description requirement.

**III.** Whether a new trial on obviousness is required because the district court erroneously granted judgment as a matter of law (JMOL) to Amgen on Appellants' obviousness defense.

**IV**. Whether Appellants are entitled to JMOL on written description or enablement based on the legal insufficiency of Amgen's evidence.

**V.** If this Court affirms the liability judgment, whether the district court improperly ordered a permanent injunction.

## INTRODUCTION

This is a patent dispute between innovators who independently discovered different antibodies with different chemical structures. Both antibodies reduce cholesterol by targeting a protein, PCSK9, that causes the destruction of liver cell receptors that extract LDL ("bad") cholesterol from the bloodstream. Both antibodies are FDA-approved—Appellants' is marketed under the name Praluent, and Amgen's as Repatha. While thousands of patients rely on each medication to reduce their risk of heart attacks and strokes, only Praluent is FDA-approved in a "low dose" version, with no available substitute.

Appellants patented Praluent's amino acid sequence, the long-accepted way to claim a biological discovery. Amgen too initially patented Repatha by claiming Repatha's (substantially different) amino acid sequence. But years later—and after making and experimenting with Praluent—Amgen sought and obtained *additional* patents that broadly claim *all* antibodies that perform a particular function: binding to specific residues on PCSK9 and blocking PCSK9 from binding to liver cell receptors. Of the vast number of diverse species that fall within Amgen's broadly claimed genus, the specification discloses only two. Amgen then asserted its earlier priority date and sued Appellants, claiming that Praluent infringes its functional genus claims.

It is hard to imagine a more brazen example of a patentee who "claims more than he has invented"—precisely what the written description requirement is designed to prevent. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014) (quoting *O'Reilly v. Morse*, 56 U.S. 62, 120-21 (1853)). Yet a jury determined that Amgen's patents are not invalid, and the district court took the extraordinary step of ordering Praluent off the market.

This remarkable outcome was possible only because of a series of erroneous legal rulings by the district court. In a decision incompatible with precedent and common sense, the court prevented Appellants from introducing Praluent—the very product accused of infringement—and other structurally dissimilar PCSK9 antibodies into evidence to demonstrate that Amgen's claims lacked sufficient written description and enablement. It then permitted the jury to uphold validity based on a "newly characterized antigen" theory of written description that is both scientifically and legally flawed and unsupported by the evidence. And it eviscerated Appellants' obviousness defense with a novel extension of precedent following one-page briefing, subsequently granting Amgen's JMOL motion on non-obviousness without allowing Appellants to respond.

Any of these errors is independently sufficient to vacate and remand for a new trial. But Amgen's claims are also invalid as a matter of law, warranting outright reversal. The crux of Amgen's case is that disclosing binding sites on an *antigen* necessarily describes *all antibodies* that bind there. As a matter of science, that contention is no more defensible than the proposition that describing the location of a parking spot describes all vehicles that fit into it. To make matters worse, the antigen (PCSK9) and the usefulness of an antibody that binds to it were well-understood. Amgen did little more than identify the amino acids where antibodies bind, using well-known x-ray crystallography techniques, without providing methods for making additional antibodies that satisfy the claims. By claiming all antibodies that perform a certain function based on a mere description of that function, Amgen seeks to "preempt the future before it has arrived." *Id.* at 1301.

The district court's medicine-removing injunction is likewise indefensible. The court ordered Praluent permanently removed from the market, even though it expressly found that doing so would *disserve* the public interest, thus squarely contradicting Supreme Court precedent holding that a plaintiff "*must* demonstrate … that the public interest *would not be disserved* by a permanent injunction." *eBay Inc. v. MercExchange L.L.C.*, 547 U.S. 388 (2006) (emphases added). The court, moreover, provided no justification for its inexplicable conclusion. And its apparent belief that lifesaving medicine must be taken away from patients despite the availability of money damages to remedy any harm is a paradigmatic abuse of discretion.

Throughout the proceedings below, the district court candidly acknowledged struggling with the issues, repeatedly expressed concerns about its decisions, and admitted leaving many legal issues for this Court's determination. The court's no-confidence vote in its own rulings is well-taken, as is this Court's decision to stay the injunction pending appeal. The deeply flawed judgment should be vacated or reversed. At a minimum, the equally flawed injunction should be vacated.

## STATEMENT OF THE CASE

### A. Factual Background

High levels of low-density lipoprotein cholesterol (LDL-C), or "bad cholesterol," cause heart attacks, strokes, and cardiovascular disease—the world's leading cause of death. Appx2417(394:20-395:17). Doctors have long treated high LDL-C with small molecules called statins. Appx2420(405:1-4). But in some cases, statins have adverse side effects or cannot reduce a patient's LDL-C to a healthy level, requiring alternative treatment. Appx2420(405:25-407:22).

One such treatment is a PCSK9 inhibitor—the medicine at issue here. PCSK9 (proprotein convertase subtilisin/kexin type 9) is a naturally occurring protein that binds to and causes the destruction of liver cell receptors (LDL receptors, or LDL-Rs) responsible for extracting LDL-C from the bloodstream. Appx1200(391:18)-Appx1202(400:3). In the early 2000s, academic researchers discovered PCSK9's harmful effects. *See* Appx1953; Appx1197(379:20)-

Appx1202(399:10). Building on that knowledge, pharmaceutical companies sought a product that could block PCSK9 from binding to LDL-Rs, thereby sparing LDL-Rs from destruction and decreasing bad cholesterol levels.

Rather than pursuing "small molecules" like statins, researchers pursued antibodies—large, complex proteins that target a particular antigen like PCSK9. Appx2410(366:1-4); *see AbbVie*, 759 F.3d at 1290-91 (describing antibodies). An antibody is comprised of amino acids and consists of "four chains" (two "heavy" and two "light") arranged in a Y-shape and "folded into a three-dimensional structure." *AbbVie*, 759 F.3d at 1290-91. An antibody's amino acid sequence determines its three-dimensional structure, which in turn determines its antigen-binding characteristics, *i.e.*, what the antibody is and does. *Id.* at 1301; Appx1257(615:12)-Appx1258(616:12).

More specifically, an antibody's binding characteristics are determined by the sequence of amino acids in each chain's "variable region," the "portion of the antibody … that binds to the antigen." *AbbVie*, 759 F.3d at 1291. Each variable region "has three complementarity determining regions ('CDRs')." *Id.* The CDRs "interact closely with" an antigen's "epitope"—the precise binding site on the antigen. *Id.* Accordingly, the amino acid sequence of the variable regions, particularly the CDRs, "really … determines what the antibody is." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1345 (Fed. Cir. 2011).

### 1. Appellants' Praluent

Appellants began work on a PCSK9-inhibiting antibody in 2007. Appx1193(362:21-23). Appellants' scientists injected PCSK9 into mice genetically engineered to produce human antibodies in response to a foreign antigen. Scientists collected the antibodies and used screening processes called "assays" to determine which antibodies bound to PCSK9 and blocked its binding to LDL-Rs. Appx2410(366:16-367:19). They then tested the most promising antibodies in animals, which showed substantial reductions in LDL-C. Appx2410(367:15-22).

In June 2008, Appellants selected several lead candidates for use as therapeutic antibodies, and in February 2009 moved forward with clinical development of alirocumab, later known as Praluent. Appx2410(368:2-10). In November 2011, the Patent and Trademark Office (PTO) issued Appellants a patent that claimed Praluent by its amino acid sequence. U.S. Patent No. 8,062,640 at 457:14-458:17; *see* Appx2414(374:1-4).

Following successful clinical trials, Appellants sought FDA approval in November 2014. Appx2412(375:10-19). To get Praluent to patients faster, Appellants purchased a congressionally-created "priority review voucher" to expedite the FDA review process. Appx2294-96; *see* 21 U.S.C. §360ff.[2] FDA

[2] Amgen considered purchasing the same voucher. Appx2365(185:13-186:7).

approved Praluent in July 2015, making Praluent the first PCSK9 inhibitor on the market. Appx1193(364:6-10).

FDA approved Praluent in two doses: a 75-mg biweekly "low dose" that reduces LDL-C by approximately 45 percent, and a 150-mg biweekly "high dose" that reduces LDL-C by approximately 60 percent. Appx2392(294:22-295:3). The dosing choice is significant, because most doctors "treat to target." Appx2384(263:5-13); Appx2422(415:2-15). That is, they aim to reduce a patient's bad cholesterol to, *but not below*, a certain level, because "too low" LDL-C has uncertain long-term medical effects. Appx2422(413:9-16). The FDA label for Praluent accordingly recommends that doctors start patients on the low dose and states that the "long-term effects of very low levels of LDL-C … are unknown." Appx2297. Doctors have prescribed Praluent more than 100,000 times, with about 85 percent of those prescriptions for the low dose. DE14-20¶¶7,9.

### 2. Amgen's Repatha

While Appellants were developing Praluent, Amgen was pursuing its own PCSK9-inhibiting antibody. Amgen injected PCSK9 into mice, collected the antibodies generated, and used assays to screen for antibodies that bound to PCSK9 and blocked binding to LDL-Rs. Appx1286(730:3)-Appx1289(743:18); Appx1167(259:4)-Appx1170(271:5). Amgen ultimately isolated its own lead candidate—evolocumab, later known as Repatha. Appx1173(283:2)-

Appx1174(288:11); Appx1184(327:1-5). The PTO issued Amgen a patent that claimed Repatha by its amino acid sequence in October 2011. U.S. Patent No. 8,030,457. Amgen obtained FDA approval for Repatha in August 2015. Appx1175(293:2-4).

Unlike Praluent, Repatha is not FDA-approved in doses providing different levels of LDL-C reduction. Rather, Repatha is approved only in 140-mg biweekly and 420-mg monthly doses, both of which reduce LDL-C by about 60 percent. Appx2340(88:9-16); Appx2346(111:17-112:1). Like Praluent's label, the FDA-approved label for Repatha states that the "long-term effects of very low levels of LDL-C … are unknown." Appx2264-2265.

**B. The Patents-in-Suit**

This case does *not* involve Amgen's patent claiming Repatha by its amino acid sequence. Praluent does not infringe that patent. Rather, this case involves two *additional* patents obtained by Amgen three years later—U.S. Patent Nos. 8,829,165 ('165 patent) and 8,859,741 ('741 patent). Appx153-537; Appx538-923.

The patents-in-suit do not claim Repatha—or any other antibody—by amino acid sequence. Instead, the relevant claims cover the entire genus of antibodies that bind to specific amino acid residues on PCSK9 and block PCSK9 from binding to LDL-Rs.[3] Claim 2 of the ’165 patent is representative. It claims an “isolated monoclonal antibody … wherein the monoclonal antibody binds to at least” the residue S153 and “blocks binding of PCSK9 to LDLR.” Appx528(427:46-55); *see also* Appx528(427:64-65, 428:45-46, 428:60-61) (claims 7, 9, and 15 claiming isolated monoclonal antibodies that bind to at least one specified residue and block binding of PCSK9 to LDL-Rs).[4]

The patents share a specification that discloses the trial-and-error process Amgen used to generate and screen antibodies that bind to PCSK9 and block PCSK9 from binding to LDL-Rs. Appx351(73:29)-Appx376(124:31). The specification also discloses the three-dimensional structures, obtained via x-ray crystallography, of two antibodies known to bind to residues recited in the claims—21B12 (Repatha) and 31H4. Appx176(Fig.3E); Appx207(Fig.3JJ); Appx364(99:29)-Appx366(103:60). Finally, the specification discloses the amino

[3] A “residue” is a particular amino acid along PCSK9’s amino acid sequence. Thus, the residue “S153” refers to the amino acid serine, located at the 153rd position of PCSK9’s sequence. *See* Appx1202(400:8-11); Appx1209(428:14-16).

[4] Similarly, Claim 19 covers an isolated monoclonal antibody that binds to at least *two* specified residues and blocks binding of PCSK9 to LDLR. Appx529(429:7-11). Claim 29 covers a “pharmaceutical composition comprising an isolated monoclonal antibody” that binds to at least two specified residues and “blocks the binding of PCSK9 to LDLR by at least 80%.” Appx529(430:17-23). And Claim 7 of the ’741 patent recites an “isolated monoclonal antibody” that “binds an epitope on PCSK9 comprising at least one of” two specified residues and that “blocks binding of PCSK9 to LDLR,” “wherein the isolated epitope is a functional epitope.” Appx913(427:36-42, 56-57).

acid sequences of 22 other antibodies that "bin" with Repatha or 31H4, meaning they allegedly "compete" with these antibodies for binding to PCSK9. Appx168-171(Figs.2A-2D); Appx172-207(Figs.3A-3JJ); Appx358(88:30)-Appx359(89:37). The specification indisputably does not demonstrate (*e.g.*, through x-ray crystallography) where any of the 22 other antibodies actually binds to PCSK9. Appx1325(880:1-9).

### C. Procedural History

#### 1. Pretrial Proceedings

In October 2014, Amgen sued Appellants, claiming that Praluent infringed the '165 and '741 patents. Appellants stipulated to infringement of Amgen's broad, functional claims but challenged their validity on written description, enablement, and obviousness grounds.

At a February 2015 scheduling conference, Amgen proposed and the court agreed to forgo preliminary injunction proceedings in exchange for an expedited trial in early 2016. Appx932(9:1-18), Appx934(11:17)-Appx935(12:3); Appx964. Given the aggressive timetable, the court required the parties to argue their legal disputes largely through *Daubert* motions decided shortly before trial. The court later expressed regret about that approach. *See, e.g.* Appx1405(1076:9-15) (observing that "this case could have benefited from a summary judgment practice"). That regret was well-founded, as the court improperly resolved two critically important issues shortly before trial on limited briefing.

**a. Exclusion of Post-Priority-Date Evidence**

The district court's most significant pretrial ruling/error came on Amgen's motion to exclude Appellants' evidence about antibodies developed after the patents' undisputed priority date of January 9, 2008. To support its written description defense that Amgen had not disclosed either a "representative number of species falling within the scope of the genus" or "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus," *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc), Appellants intended to show that Praluent and other post-priority-date antibodies encompassed by Amgen's genus claims were substantially different in structure from the antibodies disclosed in Amgen's specification. Appellants invoked this Court's decision in *AbbVie*, which upheld an invalidity verdict because the specification failed to disclose "some species representative of antibodies that are structurally similar to" the accused product. 759 F.3d at 1301. Appellants also intended to prove lack of enablement by demonstrating that Amgen struggled for years after 2008 to find additional antibodies within the genus.

In a four-paragraph ruling issued three weeks before trial, the district court excluded the evidence, invoking its "broad leeway" to determine whether the evidence "will help the jury understand" the relevant issues. Appx994¶5; *see* Appx992-995¶¶3-6. When Appellants requested reconsideration, the district court acknowledged that it was "struggling," Appx1003(14:19-20); Appx1004(18:19-20), and expressed concern that it had "swept too much information away," Appx1004(19:1-2). The court nevertheless affirmed its decision to exclude Appellants' evidence of post-priority-date antibodies (like Praluent) with structures very different from the antibodies disclosed in Amgen's patents. Appx1001(9:21-23). The court rejected Appellants' reliance on *AbbVie*, stating that "the Federal Circuit arguably departed from its own precedent" in deciding *AbbVie* and electing instead to follow *In re Hogan*, 559 F.2d 595 (C.C.P.A. 1977). Appx1032-1033¶¶2-3.[5]

**b. Exclusion of Prior Art References**

The district court also issued a pretrial ruling eviscerating Appellants' obviousness defense. Appellants had argued that Amgen's asserted claims were obvious in view of published PCT applications by Novartis and Schering, each of which claimed priority to a provisional application predating Amgen's priority date. *See* Appx1963; Appx2056. Amgen contended that under *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015),

[5] The district court subsequently extended its ruling to enablement. *See* Appx1315(843:8)-Appx1318(854:22).

Appellants could claim priority only if they proved that the specifications of those provisional applications provided full-blown written description and enablement support for the subsequent PCT applications' claims. Appx1012(52:2)-Appx1015(64:19).

After ordering one-page "briefing," Appx1015(62:16-22); Appx1028(117:23)-Appx1029(118:7), the court adopted Amgen's *Drinkware* interpretation. Accordingly, it instructed Appellants to "supplement [their] expert reports to appropriately address the question of whether the Schering and Novartis references constitute prior art by comparing their claims to the prior disclosures." Appx1037. Appellants prepared a supplemental report, but, as discussed *infra*, when Amgen subsequently moved for JMOL on non-obviousness, the court invoked its *Drinkware* ruling and granted JMOL without even allowing Appellants to respond.

### 2. Trial Proceedings

During trial, the district court continued to "struggl[e]" with the issues. Appx1316(846:21); Appx1410(1094:6-10). The court also repeatedly second-guessed its decisions, *e.g.*, Appx1405(1076:9-1077:6), and remarked that "the Federal Circuit is going to have lots to think about," Appx1371(1065:20-21).

#### a. Written Description and Enablement

Despite having the core of their case excluded, Appellants presented their written description and enablement defenses to the jury. As to written description, Appellants' experts explained that Amgen's specification does not disclose any "structural features common" to the broad, functionally defined genus. *Ariad*, 598 F.3d at 1350. As Dr. Eck explained, the function that defines the genus—binding to certain amino acids on PCSK9—"does not tell you anything at all about the structure" of members of the genus. Appx1241(549:5-6). That is because, as a matter of science, it is "just not possible" to determine an antibody's structure based on where that antibody binds to an antigen. Appx1241(549:11).

Amgen did not dispute the basic science underlying this testimony. Its expert, Dr. Rees, nevertheless suggested that antibodies that bind in the same place "must share structural features … that allow them to get the shape fitting that is required." Appx1332(908:20-24). Amgen offered no scientific basis for that circular redefinition of "function" as "structure." As Dr. Eck explained, the surface of PCSK9 is not "somehow a mold that tells us what the structure of the antibody that binds to it in a particular place has to be. It just does not work that way." Appx1414(1111:9-11). Amgen's expert Dr. Petsko admitted as much. When asked for an opinion about Appellants' position that "you can't predict" structure based on an antibody's binding site, Dr. Petsko responded, "My opinion is they're right." Appx1314(836:9-11).

In analyzing whether the specification described a "representative number of species," *Ariad*, 598 F.3d at 1350, Appellants' expert testified that "the claims in the patent are very broad" and "cover a large number of antibody structures." Appx1257(612:12-17). Amgen expert Dr. Petkso agreed that there can be "many, many antibodies" that bind the residues recited in Amgen's claims, limiting his estimation to just short of "infinite." Appx1322(869:14-16, 868:6-11). He also agreed that, of those many, many antibodies within the claimed genus, the specification discloses only *two* antibodies known to satisfy the claims: 21B12 (Repatha) and 31H4. Appx1265(644:24-645:13); Appx1325(882:5-8); Appx1339(937:21-25).

Amgen countered that it had disclosed 22 other antibodies that purportedly "bin" with—that is, compete for binding on PCSK9 with—21B12/Repatha or 31H4. Appx1309(819:5)-Appx1310(820:9); Appx1310(823:15)-Appx1311(824:10). But Amgen's own experts admitted that they did not actually know whether any of those 22 "co-binning" antibodies satisfied the claims, because they could not tell which residues on PCSK9 the "co-binning" antibodies actually bind. Appx1252(594:23-595:3); Appx1254(600:22-601:3). Regardless, as Appellants' expert explained, many of the co-binning antibodies have "essentially the same" amino acid sequence as 21B12/Repatha, so even if they did bind the claimed residues, they would not help show that Amgen's disclosure is representative of the claimed genus. Appx1243(558:12-19).

Appellants' experts also testified that Amgen's specification does not satisfy the enablement requirement. As Dr. Siegel explained, the specification at best explains how to engage in the same "very unpredictable," trial-and-error process that Amgen used to identify the two claim-satisfying antibodies out of the thousands it initially isolated. Appx1269(662:23-663:22). Determining whether an isolated antibody falls within the claims, furthermore, requires using the difficult and uncertain technique of x-ray crystallography, and some antibodies cannot be crystallized at all. Appx1241(549:17)-Appx1242(552:2); Appx1265(645:4-13); Appx1313(833:10-11); Appx1319(858:10-18). Finally, even those isolated antibodies "wouldn't be useful" in making the "full scope" of the invention, *i.e.*, other antibodies meeting the claims, because—as noted—knowing where an antibody binds does not tell a scientist how to make the antibody. Appx1272(673:3-7). Amgen's experts again confirmed as much, admitting that scientists *cannot* use a "binding portion" of PCSK9 to make the antibodies, "because you can't tell an immune system just to make antibodies to" a binding site. Appx1340(941:24-942:3).

**b. Obviousness**

Appellants also presented extensive expert testimony on the obviousness of Amgen's claims. Dr. Ravetch testified that, among other things, the Novartis and Schering PCT applications disclose isolated monoclonal antibodies that inhibit

PCSK9 binding to LDL-Rs, and how to make and identify such antibodies. Appx1211(434:6)-Appx1216(457:9); Appx1971; Appx1974; Appx1985; Appx2011; Appx2041; Appx2058; Appx2075; Appx2080-2081. Dr. Ravetch also testified that these references disclose 12 of the 15 amino acids of PCSK9 recited in the claims at issue, and that isolated monoclonal antibodies that bind to at least one of those amino acids will block PCSK9 binding to LDL-Rs. *Id.*

Following Appellants' case-in-chief, Amgen moved orally for JMOL on obviousness. Appx1285(725:20-726:6). The district court stated it would "reserve judgment" and there was "[n]o need for [Appellants] to even respond." Appx1285(726:7-8). Amgen followed with a written JMOL motion, arguing that the Novartis and Schering PCT applications were not prior art under the court's *Drinkware* interpretation. Appx1374-1379. The very next trial day, the court, invoking its *Drinkware* ruling, granted JMOL to Amgen on non-obviousness without even giving Appellants an opportunity to respond. Appx1405(1077:2-3).

#### c. Jury Instructions

The parties agreed to jury instructions stating that written description can be satisfied by either the "representative number of species" or "common structural features" tests. But the district court also permitted the jury to rely on the so-called "newly characterized antigen" theory, under which written description can be satisfied "by the disclosure of a newly-characterized antigen … if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine." Appx1584. The district court overruled Appellants' objection, Appx1370(1063:11-12), though it later described its ruling as not "clearly the law," Appx1452(1268:20-24).

### 3. Verdict, Post-Trial Motions, and the Permanent Injunction

The jury rejected Appellants' invalidity defenses. Appx1586-1589. Appellants filed post-trial motions for JMOL on written description and enablement and for a new trial on all of its defenses. Despite forfeiting a preliminary injunction, Amgen sought a permanent injunction removing Praluent from the market. Appx2313-2318. The district court held a two-day hearing during which the parties presented testimony whether Amgen had satisfied its burden under *eBay*.

Nine months later, the district court denied Appellants' post-trial motions and issued a seven-page order granting a permanent injunction. Appx35-64; Appx28-34. With almost no analysis, the court found that Amgen had suffered irreparable harm, that Amgen had no adequate remedy at law, and that the balance of harms was "neutral." Appx32-33¶¶7-9. It then found that the public interest "weighs in favor" of *Appellants* and that "the public interest of having a choice of drugs should prevail." Appx32-33¶¶10-12. But without explaining how an injunction that *disserves* the public interest could be consistent with *eBay* or equity, the district court pronounced that Amgen's "motion for a permanent injunction … is granted." Appx34¶12.

This Court stayed the injunction pending appeal. DE59.

## SUMMARY OF ARGUMENT

**I.** A new trial is required because the district court erroneously prevented Appellants from introducing their Praluent antibody—the very product accused of infringement—and other antibodies within the claimed genus that differ significantly in structure from the antibodies disclosed. This evidence would have vividly demonstrated that Amgen's patents fail to satisfy the written description requirement. The district court's categorical exclusion of post-priority evidence for inventors and accused infringers alike is illogical, unfair, and would effectively nullify the written description requirement for functional genus claims by making it almost impossible to define the scope of the genus. The district court's ruling is also foreclosed by *AbbVie*, which required a description of antibodies structurally similar *to the accused product*. The court also wrongly prevented Appellants from introducing critical post-priority evidence underscoring the patents' lack of enablement. The court's legally erroneous rulings excluded evidence so central to Appellants' written description and enablement defenses that a new trial is required.

**II.** A new trial is independently warranted because the district court erroneously instructed the jury that the written description requirement is satisfied if Amgen disclosed a "newly characterized antigen." The notion that a patentee can claim an *antibody* by describing an *antigen* is incompatible with the statutory command that a patentee provide a written description *of the invention*. The instruction has no grounding in common sense; one does not describe an arrow by describing a target. The instruction has no foundation in science; it is undisputed that describing an antigen tells one nothing about the structure of antibodies that bind to it. The instruction has no support in precedent; this Court has never affirmed a finding of validity based on a newly characterized antigen theory. And while the Court has mentioned the concept in dicta, the foundation of that dicta—PTO training materials—was recently withdrawn. Furthermore, the instruction in this case was not even consistent with that dicta. And whatever might conceivably remain of the "newly characterized antigen" instruction, Amgen's evidence did not satisfy it.

**III.** A new trial is also required because the district court eviscerated Appellants' obviousness defense based on an erroneous application of *Drinkware*. *Drinkware*, which addressed a *patent*, should not require an *application* to support its published claims with a priority application to qualify as §102(e) prior art as of the priority date. But even assuming *Drinkware* can be extended to patent applications, the district court erred again when—without giving Appellants a chance to respond, and absent any written justification—it granted JMOL to Amgen on non-obviousness, apparently but incorrectly believing that *Drinkware* requires a full-blown written description and enablement analysis for prior art.

**IV.** This Court can and should conclusively resolve this litigation by granting JMOL for Appellants on written description or enablement. At its core, Amgen's position is that describing a binding site on PCSK9 suffices to claim the entire genus of antibodies that bind there and block binding to LDL-Rs. But the undisputed science disproves that contention. Amgen's transparently circular argument that the claimed antibodies share the common *structural* feature of having the same *function* (binding to particular residues) reveals the irremediable flaw in its overbroad and innovation-chilling functional genus claims. Amgen's patents simply reformulate the problem to be solved (isolating antibodies that bind to specific residues and block binding of PCSK9 to LDL-Rs) rather than formulating a solution. While Amgen used routine methods to isolate antibodies, the hard work of characterizing the structurally diverse antibodies remains. And even upon undertaking this work, one may not arrive at a requisite number of antibodies sufficient to enable the full scope of the claims. This is exactly the type of "undue experimentation" this Court has held *not* to support enablement.

**V.** Even if this Court were to affirm on liability, it should vacate the permanent injunction. The district court ordered Praluent's removal from the market despite expressly finding that doing so would disserve the public interest. That determination is irreconcilable with *eBay*—which unambiguously requires a plaintiff to demonstrate that an injunction would *not* disserve the public interest—and basic principles of equity. Worse still, the district court offered literally no explanation for granting an injunction concededly against the public interest. Finally, revoking a lifesaving drug from patients with no equivalent substitute, in conceded disservice of the public interest, when the ordinary remedy of money damages is readily available, is a paradigmatic abuse of discretion.

## STANDARDS OF REVIEW

This Court reviews a district court's rulings on "nonpatent issues" under "the law of the circuit in which the district court sits"—here, the Third Circuit. *Fujifilm Corp. v. Benun*, 605 F.3d 1366, 1370 (Fed. Cir. 2010). The Third Circuit reviews evidentiary rulings for abuse of discretion. *See Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1341 (Fed. Cir. 2009). A district court "necessarily abuse[s] its discretion" if "it base[s] its ruling on an erroneous view of the law." *Highmark Inc. v. Allcare Health Mgmt. Sys., Inc.*, 134 S. Ct. 1744, 1748 n.2 (2014).

The Third Circuit reviews "jury instructions de novo." *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1292 (Fed. Cir. 2015). It "exercises plenary review over a district court's rulings on motions for JMOL." *Rothman v. Target Corp.*, 556 F.3d 1310, 1316 (Fed. Cir. 2009).

This Court reviews "a district court's decision to grant a permanent injunction for abuse of discretion." *Acumed LLC v. Stryker Corp.*, 551 F.3d 1323, 1327 (Fed. Cir. 2008). A legal error or "clearly erroneous assessment" of evidence is "necessarily" an abuse of discretion. *Highmark*, 134 S. Ct. at 1748 n.2.

## ARGUMENT

### I. The District Court's Exclusion Of Post-Priority-Date Evidence, Including Praluent And Other Antibodies Within Amgen's Functionally Claimed Genus, Was Prejudicial Error And Requires A New Trial On Written Description And Enablement.

#### A. A New Trial Is Required on Written Description.

The written description requirement of 35 U.S.C. §112 exists to ensure "that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351. To show invention, a patentee must convey in its disclosure that it "had possession of the claimed subject matter as of the filing date." *Id.* at 1350. Demonstrating possession "requires a precise definition" of the invention, "such as by structure, formula, chemical name, or physical properties." *Id.* To provide this "precise definition" for a claim to a genus, a patentee must disclose "a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* "Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support," *AbbVie*, 759 F.3d at 1301, because such claims "may simply claim a desired result … without describing species that achieve that result"—an impermissible "attempt to preempt the future before it has arrived," *Ariad*, 598 F.3d at 1349, 1353.

Here, Amgen claims to have invented the genus of antibodies that bind to specified residues on PCSK9 and block binding to LDL-Rs, precisely the kind of functional genus claim "inherently vulnerable to invalidity challenge for lack of written description support." *AbbVie*, 759 F.3d at 1301. Amgen accused Praluent of falling within the claimed genus, alleging in substance that Amgen invented Praluent. Appellants stipulated to infringement, but argued that Amgen's patents lack sufficient description to support a claim to inventing the genus. The critical question at trial was thus whether Amgen disclosed "a representative number of species falling within the scope of the genus or structural features common to the members of the genus." *Ariad*, 598 F.3d at 1350.

Answering that question necessarily required a comparison between the "structure, formula, chemical name, or physical properties" of the antibodies disclosed in Amgen's patents and others "within the scope of the genus." *Id.* Appellants planned to show substantial differences between the disclosed antibodies and the one antibody indisputably "within the scope of the genus"—the accused product, Praluent. For example, Appellants' experts would have testified that the CDRs of Praluent and Repatha—the key portions of the antibodies that govern where the antibodies bind—share only 26 percent sequence identity, while the CDRs of Praluent and the only other disclosed antibody known to meet the claims (31H4) share only 30 percent sequence identity. Appx1733¶54. They also would have testified that Praluent is very dissimilar in structure to the other 22 "co-binning" antibodies disclosed in the specification that, according to Amgen, "more likely than not" meet the claims. *See* Appx1734-1736¶¶57-63; Appx1623-1624¶¶67-74; Appx1850-1867¶¶33-49; Appx1325(880:7). Moreover, they would have testified that Praluent is closer in structure to antibodies targeting the influenza and rabies viruses than it is to Repatha. Appx2452. On top of that, Appellants' experts intended to show the jury that several *other* antibodies developed by third parties and known to satisfy the claims (via x-ray crystallography) also are not structurally similar to any antibodies disclosed by Amgen. *See* Appx1898-1913¶¶21-32; Appx1739-1745¶¶75-89; Appx1630-1631¶¶90-96.

This evidence of substantial structural variability among numerous antibodies undeniably "within the scope of the genus" would have been devastating to Amgen's assertion that its patents sufficiently described species "representative" of the genus. *Ariad*, 598 F.3d at 1350. And this scant and homogeneous disclosure certainly would not allow a skilled artisan to "visualize or recognize" members of this broad and diverse genus, like Praluent. *Id.* Yet the district court, in a decision that it concededly struggled with and repeatedly second-guessed, excluded all this evidence "because the written description requirement is tested as of the filing date." Appx1030-1031.

The district court's decision is flawed on many levels. First, because the *inventor* must demonstrate possession of the invention "as of the filing date," Appx1030-1031, evidence of what the *inventor* discovered afterward is irrelevant to written description, *see Ariad*, 598 F.3d at 1355. But neither the district court nor Amgen cited any authority for the court's rule that an *accused infringer* cannot use post-priority-date evidence to demonstrate the variability of broad functional genus claims. And for good reason: confining an accused infringer to pre-priority-date evidence would make it extremely difficult to establish "the scope of the genus" that the patentee is required to describe. Indeed, it is almost always the case that the accused product and any other product within the claims will have arisen *after* the priority date; otherwise, the products would anticipate the patent claims. *See Brown v. 3M*, 265 F.3d 1349, 1352 (Fed. Cir. 2001) ("That which infringes if later anticipates if earlier."). The district court's categorical rule would require an accused infringer like Appellants to prove something with nothing.

That is not the law. Quite the contrary, this Court has long explained that the written description requirement protects against "attempt[s] to preempt the future before it has arrived." *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993). A patentee *cannot* "recite a description of the problem to be solved while claiming all solutions to it," including "any compound *later actually invented* and determined to fall within the claim's functional boundaries." *Ariad*, 598 F.3d at 1353 (emphasis added). Indeed, Amgen itself has recognized that "the written description requirement … protects future innovation against unjustified preemption." Amicus Br. for Amgen Inc. 7-8, *Ariad*, No. 2008-1248 (Fed. Cir. Nov. 19, 2009). None of that would make any sense if future innovators were barred from introducing evidence of their own innovations in written description challenges. Handing patentees such an advantage in infringement litigation would be profoundly unfair, choke off innovation, and conflict with the axiomatic rule that "claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001); *see id.* ("A patent may not, like a nose of wax, be twisted one way to avoid anticipation and another to find infringement.").[6]

[6] It would be particularly unfair to preclude Appellants from introducing Praluent here, because Amgen concededly made and experimented with Praluent when drafting the asserted claims. Appx1230(504:18-506:20).

*AbbVie* clearly demonstrates the district court's error. There, as here, the accused infringer of a functional claim to a genus of antibodies stipulated to infringement and challenged validity based on written description. As here, the challenger in *AbbVie* argued that the "functionally defined claims cover antibodies having widely varying structures including" the accused antibody, and that the antibodies disclosed in the patents "are not representative of the entire genus." 759 F.3d at 1298. But unlike here, the challenger in *AbbVie* was permitted to introduce its own accused antibody to show the jury that it "differ[ed] considerably from the … antibodies described in [the asserted] patents." *Id.* at 1300. The jury found the patents lacked adequate written description, and this Court affirmed because a patentee asserting a functional genus claim based on representative species "must at least describe some species representative of antibodies that are structurally similar to [the accused product]." *Id.* at 1301.

This Court in *AbbVie* never once considered whether the accused antibody preceded or postdated the priority date, even though that very question had been vigorously litigated as part of an anticipation defense. The district court had found that there was a genuine dispute of fact on the question, *see Abbott GMBH & Co., KG v. Centocor Ortho Biotech, Inc.*, 870 F. Supp. 2d 206, 245 (D. Mass. 2012), but that factual dispute was not material to written description (as opposed to anticipation); this Court found the patent invalid on written description grounds without addressing that question. If the priority date mattered to the relevance of the accused antibody for written description purposes, *AbbVie* surely would have mentioned it.

The district court here recognized the tension between its ruling and *AbbVie*, but, remarkably, accused this Court of "arguably depart[ing] from its own precedent" in *AbbVie*, and decided that it should "limit [*AbbVie*] to its unusual facts and procedural posture." Appx1032-1033. The "precedent" that the district court had in mind—one it apparently considered more relevant to this case than the 2014 *AbbVie* decision analyzing the written description requirement for functional genus claims to antibodies—was a 1977 decision by this Court's predecessor involving an enablement challenge to a patent for "solid polymers of olefins." *Hogan*, 559 F.2d at 597.

*Hogan* has no bearing on this case. The issue in *Hogan*—an enablement (not written description) case arising from a PTO Board of Appeals rejection (not an infringement accusation)—was whether it was permissible for an examiner to use a change in the "state of the art" after the priority date as evidence to support a rejection for lack of enablement. *Id.* at 597, 600. Hogan claimed a solid polymer of polypropylene, which was broad enough to encompass either crystalline or amorphous polyproylene—the latter of which did not exist until years after Hogan's priority date. *Id.* at 597-98. The PTO rejected Hogan's application because it did not enable production of amorphous polypropylene. *Id.* at 601, 605. This Court reversed, explaining that compliance with the enablement requirement was to be measured by the *state of the art* as of the filing date, not on post-priority-date changes in the state of the art. *Id.* at 604-05. But *Hogan* never suggested that post-priority-evidence on the *scope of the claims* is impermissible, which makes it inapplicable to this case.

Moreover, this Court has repeatedly cautioned against over-reading *Hogan*. In *Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.*, this Court relied on post-priority-date evidence that revealed the state of the art at the time of filing to evaluate enablement. 315 F.3d 1335, 1340 (Fed. Cir. 2003). The Court expressly rejected arguments that reliance on the post-priority-date evidence for this purpose was foreclosed, explaining that "*Hogan* cannot be read to assist *improper* enforcement against later developers." *Id.* Similarly, this Court relied on post-priority-date evidence to uphold a written description challenge in *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004). The Court found Chiron's description of a claim to chimeric and humanized antibodies inadequate because chimeric antibodies did not exist when Chiron submitted the relevant application. *Id.* at 1254-55. The Court expressly rejected the argument that post-priority-date evidence could not be used to evaluate the adequacy of the description at the time of filing—precisely the argument the district court adopted here. *Id.* at 1260.[7]

In short, *Hogan* poses no bar to Appellants' use of their own accused antibody and other post-priority-date evidence to challenge Amgen's written description. The district court's contrary decision, resulting in exclusion of Appellants' evidence, was legal error and necessarily an abuse of discretion. *See Highmark*, 134 S. Ct. at 1748 n.2. And the district court's error was plainly prejudicial. As explained above, the exclusion of Praluent and third-party antibodies within the claimed genus prevented Appellants from showing the jury how unrepresentative of the genus the antibodies disclosed in Amgen's specification are. *See* pp. 25-27, *supra*; *Ariad*, 598 F.3d at 1350. That evidence was not only highly probative; it "was potentially [Appellants'] best evidence and not cumulative" of any evidence that Appellants were able to present. *McQueeney v. Wilmington Trust Co.*, 779 F.2d 916, 928 (3d Cir. 1985). The district court itself described the evidentiary question as "akin to a dispositive issue." Appx1003(14:19-20). A new trial on written description is accordingly required.

[7] This Court has recognized elsewhere that post-filing-date evidence can be probative of whether a patent complies with §112. *See, e.g.*, *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); *In re Goodman*, 11 F.3d 1046, 1051-52 (Fed. Cir. 1993).

### B. A New Trial Is Required on Enablement.

For many of the same reasons, the district court's improper exclusion of post-priority-date evidence requires a new trial on enablement. Under the enablement requirement, "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). To prove that a patentee has not enabled the "full scope of the claimed invention," an accused infringer must be able to introduce evidence of materials alleged to be within the claims. The district court had no more basis in logic or law to exclude Appellants' enablement evidence than its written description evidence.

The district court's ruling substantially prejudiced Appellants' enablement defense. For example, Appellants intended to present evidence that even after filing its patent, Amgen continued its previous trial-and-error search for antibodies falling within its claimed genus. In particular, Appellants were prepared to offer testimony about Amgen's post-priority-date work to develop an antibody that would bind to the middle of the claimed PCSK9 residues. Appx1387; Appx1393-1403. The fact that, for many years and with great difficulty, Amgen was still searching for antibodies fitting within the heart of its claims underscores that the patents' disclosure do not enable "the full scope of the claimed invention." And the fact that Amgen searched for those antibodies using the same laborious trial-and-error method testing thousands of antibodies, with no certainty of success, confirmed that a skilled artisan could not create and isolate the full scope of the claimed antibodies without "undue experimentation." *See* Appx1662-1663¶¶171-174. Because excluding this evidence was erroneous and prejudicial, a new trial on enablement is required.

## II. The District Court's "Newly Characterized Antigen" Instruction Requires A New Trial On Written Description.

The district court's erroneous "newly characterized antigen" instruction independently warrants a new trial. In addition to the "common structural features" and "representative species" tests for meeting the written description requirement, the district court also instructed the jury, over Appellants' objection, that:

> In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine.

Appx1580.

Amgen has conceded that this instruction could have been the basis for the jury's verdict of no invalidity, DE56-1 at 13, but there are three fatal problems with it. First, disclosing an *antigen* does not satisfy the written description requirement for a claim to an *antibody*, so the very notion of a "newly characterized antigen" instruction is unsupported by law. Second, even if some version of a "newly characterized antigen" test were valid, the instruction here omitted critical elements that would be necessary and was thus legally defective. Third, even if the instruction were proper, Amgen's evidence was insufficient to satisfy it. Each of these flaws independently requires vacatur of the verdict. *See Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1222 (Fed. Cir. 2014) (verdict must "be invalidated" if "one of the possible bases was based on *legal* error"); *SEC v. Teo*, 746 F.3d 90, 100 (3d Cir. 2014) (verdict vacated where "one of the plaintiff's theories of liability for which there was insufficient evidence might have been the one on which the jury grounded its determination of liability").

### A. The "Newly Characterized Antigen" Instruction Has No Basis in the Patent Statute, Science, this Court's Precedent, or Common Sense.

First, the verdict must be set aside because the "newly characterized antigen" instruction has no basis in law or science, and the district court accordingly erred in giving any such instruction. The most basic error is straightforward: Section 112 requires a "written description *of the invention*," but the instruction envisions a patent based on a description of something *that is not the invention*—namely an antigen, rather than the antibody that is the subject of the claims. This would be like awarding a patent to all arrows based on a description of a target. By its plain terms, therefore, the instruction contradicts the statutory text and undermines the fundamental "*quid pro quo*" of the patent system: "one describes *an invention*, and, if the law's other requirements are met, one obtains a patent." *Ariad*, 598 F.3d at 1345 (emphasis added).

This Court has refused to recognize exceptions to the written description requirement based on the subject matter of the claims. *See Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004) (noting that "the statute applies to all types of inventions"). Congress, moreover, knows how to carve out an exception to the written description requirement when it so desires. *See, e.g.*, 35 U.S.C. §162 (exempting plant patents from section 112 "if the description is as complete as is reasonably possible"). The fact that Congress has not done so with respect to antibody claims underscores that the ordinary written description rules apply.

Nor does the science support some sort of close relationship between the problem and the solution such that one might view the description of the former as an adequate description of the latter. It is undisputed science that the chemical structure of an antigen does *not* teach the structure of an antibody. *See* Appx1241(549:5-6,11); Appx1314(836:9-11). Describing an antigen does not describe an antibody, and accordingly cannot provide description for an antibody patent. *Cf. Rochester*, 358 F.3d at 925-26 (patent describing an enzyme does not constitute an adequate written description for a claim to that enzyme's inhibitors).

Contrary to Amgen's suggestion that the "newly characterized antigen" instruction reflects Federal Circuit precedent, DE56-1 at 16-17, this Court has *never once* upheld the validity of an antibody patent based solely on a description of the antigen to which the antibody binds. Amgen's position rests instead on a selective reading of an outdated provision of the PTO's *Written Description Training Materials* ("*Training Materials*")[8] that is not binding on this Court, has not been adopted in any precedential holding, does not reflect current science, and was recently withdrawn in response to this Court's clarification of the governing law.

This Court first referenced the *Training Materials* in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), a case that did not involve antibodies. The Court explained the PTO's determination in its *Guidelines*[9]—not the distinct *Training Materials*—that the written description requirement can be satisfied by disclosure of a chemical substance's "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled*

[8] PTO, *Examination Guidance and Training Materials* (Archived 2008), http://bit.ly/2kLrTLa .

[9] PTO, *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, "Written Description" Requirement*, 66 Fed. Reg. 1099 (Jan. 5, 2001).

*with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Enzo*, 323 F.3d at 964. The Court further observed that the then-applicable *Training Materials* suggested that the PTO would find adequate written description "for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." *Id.* The Court then stated that it was "persuaded by the *Guidelines*"—*not* the *Training Materials*—and proceeded to uphold the patent's validity based on the inventors' depositing the claimed gene sequences in a public depository. *Id.* at 964-65. The Court did not suggest that its passing reference to the "antibody example" in the *Training Materials* was necessary to resolve the case. Nor could it have been, since the case did not involve antibodies.

The Court actually considered antibody claims in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), but found them invalid. Specifically, the Court held that the patentee had not adequately described either the claimed antibodies or the target antigen. *Id.* at 1349. In dicta, the Court referred to *Enzo*'s one-sentence invocation of the antibody example in the *Training Materials*. *Id.*[10] The Court offered the hypothetical suggestion that if the patentee had "sufficiently described the ... antigen, he could have claimed its antibody by simply stating its binding affinity for the 'fully characterized' antigen." *Id.* But because the patentee had failed to do even that, the Court had no occasion to explore the possibility. *Id.* at 1349-50.

Although the Court's hypothetical in *Noelle* was plainly dicta, it prompted significant criticism. As commentators noted, the suggestion that a patentee could claim an antibody—or even a whole genus of antibodies—based solely on the description of an antigen "is inconsistent with the best current science" and "the actual USPTO Guidelines as well as the law." Amicus Br. for Eli Lilly 10-11, *Centocor*, No. 2010-1144 (Fed. Cir. Mar. 15, 2010). The *Guidelines* require a "known or disclosed correlation between function and structure," 66 Fed. Reg. at 1106, but the *Noelle* hypothetical would allow a patentee to claim an antibody based solely on its "function" of binding to a particular antigen. Given the absence of any inherent structural relationship between an antigen and binding antibodies, *Noelle*'s dictum "violates the logical rule of law that one cannot describe what one has not yet invented" and "stands in stark contrast to precedent." Paula K. Davis &

[10] Regrettably, the *Noelle* panel inaccurately attributed the antibody example in the *Training Materials* to the *Guidelines* and referred (in dicta) to *Enzo*'s dicta as "past precedent." 355 F.3d at 1349.

Steven P. Caltrider, *Timing (of Invention) Is Everything*, 15 Fed. Cir. B.J. 39, 64-65 (2005).

The Court again addressed antibody claims in *Centocor*. Centocor argued that this Court's "decision in *Noelle* and the PTO written description guidelines support the view that fully disclosing" a particular protein "provides adequate written description for any antibody that binds to" that protein. 636 F.3d at 1351. This Court squarely rejected that position, holding that Centocor's "suggestion is based on an unduly broad characterization of the guidelines and our precedent" and reversing the jury verdict finding the patent valid. *Id.* at 1351, 1353. The Court explained that the antibody example "discussed" in *Noelle*, *id.* at 1352—which, it skeptically noted, "[r]eferenc[ed] only an immunology text published in 1976"—"presumes that the applicant is *disclosing a novel protein* and then *claiming both the protein and an antibody* that binds to it," *id.* at 1351 (emphases added). Moreover, the antibody example assumes that production of the claimed antibodies is "conventional" and "routine." *Id.* Because the antigen in Centocor's patents was "known in the literature," and generating the claimed antibodies was not routine, the antibody example was inapplicable. *Id.* at 1352.

In sum, although this Court has "discussed" the antibody example and "newly characterized antigen" theory in several decisions, it has never upheld the validity of antibody claims based merely on disclosure of even a *novel* antigen (and

PCSK9 is not that, *see infra*). And for good reason: doing so would be contrary to both the statutory text and science. *See* pp. 35-37, *supra*. Indeed, the PTO now appears to agree: following *Centocor*, it revised the *Training Materials* "to reflect changes in the law since 2008, including any required clarifications due to developments in the law relating to 35 U.S.C. 112." PTO, *Examination Guidance and Training Materials*, http://bit.ly/2kLrTLa. The PTO released new guidance that highlights *Centocor* and conspicuously *omits* any mention of the antibody example as a means of satisfying the written description requirement. *See* DE58-5. Accordingly, the very basis for the "newly characterized antigen" theory—the misguided "antibody example"—has been superseded by not just advancements in antibody technology, but the law.

The district court's "newly characterized antigen" instruction is thus based on quicksand—or more precisely, dicta, based on subsequently-revised PTO materials, that has been undermined by subsequent precedent. This Court should reject the "newly characterized antigen" instruction as a matter of law.

### B. At a Minimum, the District Court's Version of the "Newly Characterized Antigen" Instruction Was Legally Deficient.

Even if this Court were to conclude that some form of the "newly characterized antigen" instruction is permissible in some circumstances, the verdict must still be vacated because the instruction here was legally deficient in two respects.

First, in *Centocor*, the most recent case on the subject, the Court explained that the antibody example "presumes that the applicant is disclosing a *novel* protein and then *claiming both the protein and an antibody* that binds to it." 636 F.3d at 1351-52 (emphases added). But the instruction here does not refer to a claim to "the protein," let alone a novel one. Rather, it refers only to "the case of a *claim to antibodies*." Appx1580 (emphasis added). Amgen did not request *Centocor*'s formulation, and understandably so: its patents claim only antibodies, and *not* any target protein, and any effort to claim the latter would have exposed that the relevant protein—PCSK9—is not novel. *See* Appx1320(860:6-7), Appx1320(863:24)-Appx1321(864:1).

Second, *Centocor* explained that if the "newly characterized antigen" theory applies at all, it applies "to disclosure of newly characterized antigens where creation of *the claimed antibodies* is routine." 636 F.3d at 1352 (emphasis added). But the instruction here required the jury to find only that "production of *antibodies* against such a [newly characterized] antigen was conventional or routine." Appx1580(emphasis added). In other words, the district court's instruction permitted the jury to find adequate written description if antibodies *in general* could be produced against the antigen. But that is precisely what *Centocor* found impermissible. *See* 636 F.3d at 1352. By not requiring the jury to find that production of "the claimed antibodies"—*i.e.*, antibodies that bind specific amino acids on PCSK9—was "routine," the district court omitted an essential element of the instruction as articulated by this Court in *Centocor*. *Id.*

### C. In the Alternative, There Was Insufficient Evidence to Support the Jury Verdict Under the District Court's Instruction.

In the alternative, even if the district court's instruction were correct, the evidence was insufficient to show that Amgen disclosed "a newly-characterized antigen." Appx1580.

The "antigen" to which Amgen's claimed antibodies bind is the protein PCSK9, which is *not* novel or "newly characterized." Amgen does not dispute that PCSK9 was already known when it filed its claims. Appx1216(456:12); Appx1323(874:16-24); Appx1333(913:22-914:5). The circumstances here are thus analogous to *Centocor*, where this Court rejected a "newly characterized antigen" theory because the protein was "known in the literature." 636 F.3d at 1352.

To shoehorn PCSK9 into the "newly characterized antigen" framework, Amgen's experts instead invented a new meaning for "antigen." They testified that, with respect to the Amgen patents, the "antigen" was not the full PCSK9 protein but the "region on PCSK9 to which antibodies in the patent bind"—which, not coincidentally, is exactly what Amgen claimed to have discovered. Appx1297(772:2-10). But they provided no support for this linguistically and scientifically spurious proposition, and the patents-in-suit refute it. The patents distinguish between an "antigen" and the region of an antigen to which an antibody binds, expressly defining the latter *not* as an "antigen"—as the Amgen witnesses attempted—but as an "epitope." Appx332(36:48-54). And the district court's claim construction order recognized this common sense distinction. Appx969.

Amgen's experts' own admissions further undermined their implausible definition. Dr. Petsko admitted that, in his deposition, he had agreed that the "antigen" in the Amgen patent claims is the protein PCSK9. Appx1323(872:18-873:22). He also admitted that the ordinary meaning of "antigen" to those skilled in the art is the "entire macromolecule of which the epitope is a part," and that the "most common" use of the word antigen is "the thing you inject into the mouse to get antibodies" which would be the PCSK9 protein, not just a portion of it. Appx1313(834:19-25); Appx1322(871:16-20); Appx1323(874:2-7). In addition, Dr. Petsko conceded that he had never seen a single residue referred to as an "antigen." Appx1323(875:9-13). Dr. Petsko was left to confess to having used the word antigen "sloppily," and Amgen's other expert, Dr. Rees, agreed that "there is a loose language in the use of the word antigen." Appx1322(871:10-15); Appx1335(922:6-7).

In short, a region on an antigen is no more an antigen than a fingertip is a hand. Amgen's strained effort to redefine the term was so plainly implausible that no rational factfinder could have accepted it. The only "antigen" disclosed by the claims is the complete PCSK9 protein, not an epitope on the protein. PCSK9 is not "newly characterized" and therefore cannot satisfy the district court's instruction. The verdict must accordingly be vacated.

## III. The District Court's Erroneous Grant Of JMOL Requires A New Trial On Obviousness.

A new trial is also warranted based on the district court's erroneous grant of JMOL on obviousness. To establish obviousness, Appellants intended to rely on two published PCT applications by Novartis and Schering, each of which claimed priority to a provisional application predating Amgen's priority date. But the court refused to permit Appellants to assert Novartis and Schering as prior art based on two legal errors. First, in a pre-trial ruling based on one-page "briefs," the district court wrongly extended this Court's *Drinkware* decision—which addresses priority dates of potential prior art *patents*—as applying to not just patents, but patent *applications*. The court then compounded its error when—without even permitting Appellants to respond, and without any written justification—it granted Amgen's motion for JMOL on non-obviousness, under the apparent belief that *Drinkware* requires a full-blown written description and enablement analysis for prior art. Each of these rulings is incorrect and independently warrants vacatur of the JMOL decision.

### A. The District Court Improperly Extended *Drinkware* to Published Patent Applications.

The district court's JMOL grant on non-obviousness turned on its interpretation of *Drinkware*. But *Drinkware* concerned the proof necessary to show that a *patent* asserted as prior art under §102(e)(2) was prior art as of the filing date of a parent application. *Drinkware* based its decision on *In re Wertheim*, 646 F.2d 527 (C.C.P.A. 1981), which likewise concerned a *patent* asserted as prior art. This Court has never extended the *Drinkware/Wertheim* framework to published patent *applications* asserted as prior art under §102(e)(1)—a provision that did not exist at the time *Wertheim* was decided—and nothing in precedent or policy supports such an extension.[11]

In *Drinkware*, this Court affirmed a PTAB finding that a patent challenger failed to show a reference patent was prior art under §102(e) because the challenger "failed to compare *the claims* of the [reference] patent to the disclosure in the [reference patent's] provisional application." *Drinkware*, 800 F.3d at 1381. Relying on *Wertheim*, the Court stated "[a] reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of

[11] Amgen's lone authority for applying *Drinkware* to published patent applications is a PTAB decision, *Ariosa Diagnostics, Inc. v. Illumina, Inc.*, IPR2014-01093, 2016 WL 354412 (PTAB Jan. 7, 2016), currently on appeal. *See* No. 16-2388.

the provisional application provides support for the claims in the reference patent in compliance with §112, ¶1." *Id.*

When *Wertheim* was decided, patent applications were kept confidential from the public unless and until a patent issued. As a result, potentially invalidating prior art could be secretly lurking in pending applications for years. To avoid invocation of such "secret prior art," *Wertheim* concluded that a patent qualifies as prior art under §102(e) as of the filing date of its earlier priority applications if "'but for' the delays in the Patent Office" that patent could have issued from the earlier filed application. *Wertheim*, 646 F.2d at 536-37. In *Wertheim*, the reference patent was a continuation-in-part of the relevant priority application, and because a continuation-in-part application adds new matter, the Court concluded that it was necessary to analyze whether this new matter was essential to the issued claims before the patent could qualify as prior art based on the filing date of its priority application. *Id.* at 536-39.

But the concern about "secret prior art" that drove *Wertheim* does not apply to published patent applications, which are a manifestation of Congress' solution to the "secret prior art" problem. In 1999, Congress amended 35 U.S.C. §122 to require publication of patent applications after eighteen months. Pub. L. No. 106-113, §4502, 113 Stat. 1501A-561 (1999). Because patentability is *not* a condition to publication, provisional patent applications to which priority is claimed are made publicly available once the application is published. 37 C.F.R. §1.14(a)(1)(v). As the PTO has recognized, the reasoning of *Wertheim* does not apply to published applications. *See Ex parte Yamaguchi*, 88 U.S.P.Q.2d 1606, 2008 WL 4233306, at *6-8 (BPAI 2008); *Ex parte Robbins*, No. 2009-001866, 2009 WL 3490271, at *4 (BPAI Oct. 27, 2009). And in the legislative history to the 2011 Leahy-Smith America Invents Act, Congress noted that *Wertheim* was "almost completely overruled" by the 1999 provision. 157 Cong. Rec. S1369 (daily ed. Mar. 8, 2011).

Further, the logic behind *Wertheim* was that patents that are §102(e) art must have been "ready for allowance" at time of the effective filing date, but for delays at the PTO. *See* 646 F.2d at 536. But it makes no sense to apply that logic to a published patent application, because it is prior art even if the application never issued, for example, because it claimed technology that is known or obvious. Applications are typically published with the as-filed claims, which are usually amended between filing and allowance. 37 C.F.R. §1.215. Published applications may have claims that were not patentable as filed; however, added or amended claims may be patentable after prosecution. Applying *Drinkware* to a published application with pending claims could mean that an identical disclosure could qualify as prior art one day and not the next, merely by the happenstance of usual claim amendments.

### B. Even if *Drinkware* Applied to Published Patent Applications, JMOL Was Improper.

Even if *Drinkware* applied to published applications, the district court erred in granting Amgen JMOL on non-obviousness. Amgen never disputed that the claims of the Novartis and Schering PCT applications can be traced to their provisional applications. *See* Appx2135-2145; Appx1053. Instead, Amgen argued, and the district court apparently agreed—albeit with no written reasoning, and without affording Appellants a response—that the Novartis and Schering applications could not be prior art as of their provisional application filing dates unless the applications' claims met the same full-blown written description and enablement requirements that apply to Amgen's patents. Appx1053; Appx1013(55:23-56:11). That contention is erroneous.

First, although Amgen's *patents* must show written description support for the entire breadth of their broad functional genus claims, *see Ariad*, 598 F.3d at 1350, a *prior art* reference need only disclose a species to anticipate or render obvious the genus, *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001) ("Our case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim."). Thus, it is entirely irrelevant whether the PCT applications described representative species or common structural features. Appx1217(460:14-461:3); Appx1218(462:9-19).

Second, as to enablement, disclosures in the prior art are presumed enabled. *See In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354-55 (Fed. Cir. 2003). And the enablement standard for a prior art reference under §102 is less demanding than the enablement standard under §112. *See Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005). Further, Appellants' evidence was that the Novartis and Schering PCT applications, along with other prior art, rendered Amgen's asserted claims *obvious*. Appx1215(452:19-453:4); Appx1216(456:24-457:9). Whether the Novartis and Schering PCT applications were enabled, let alone enabled by their provisional applications, is irrelevant to the obviousness inquiry because an individual prior art reference "need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein." *Amgen*, 314 F.3d at 1357.

Construing *Drinkware* to require a full-blown written description and enablement analysis for prior art, as Amgen argued and the district court apparently accepted, would result in burdensome trials-within-a-trial. Evaluating whether claims are supported by written description and enabled requires courts to construe those claims. *See Koninklijke Philips Elecs. N.V. v. Cardiac Sci. Operating Co.*, 590 F.3d 1326, 1336 (Fed. Cir. 2010); *Chiron*, 363 F.3d at 1254. Typically, a patent application is published based on the application as filed. 37

C.F.R. §1.215. Accordingly, construing the claims of a published application solely to determine the status of prior art would be particularly wasteful: a court would be required to construe published claims that may have been canceled or amended.

This is precisely why the Court has held that prior art is presumed enabled: because it is "unwise as a matter of policy to force district courts to conduct a mini-trial on the proper claim construction of a prior art patent every time an allegedly anticipating patent is challenged for lack of enablement." *Amgen*, 314 F.3d at 1355 n.21. Yet, under the district court's interpretation of *Drinkware*, such mini-trials on enablement and written description would be routine, "occupy[ing] a great deal of a [district] court's resources." *Id.* And the burdens would not end in district court. This unwarranted extension of *Drinkware* would invite mischief on appeal, where parties would challenge not only claim construction of the asserted patent, but also claim construction of prior art applications.

The far better approach, and the one consistent with this Court's precedent, is to apply a "carried forward" analysis, under which the pertinent portions of specifications in the provisional applications are carried forward into the PCT applications. *See In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010) ("[A]n applicant is not entitled to a patent if another's patent discloses the same invention, which was *carried forward* from an earlier U.S. provisional application or U.S.

nonprovisional application." (emphasis added)); *In re Klesper*, 397 F.2d 882, 885 (C.C.P.A. 1968). Here, Dr. Ravetch established that the relevant portions of the provisional specifications had been carried forward into the respective PCT applications. Appx1207(421:4)-Appx1208(422:1); Appx1208(425:11)-Appx1209(426:11). And to the extent *Drinkware* added further requirements to the "carried forward" analysis, Appellants fully satisfied them, too. *Drinkware* merely invoked "written description support," and Appellants' expert Dr. Ravetch established that representative PCT claims were identical or substantively identical to the claims in the respective provisionals and were further supported by those provisionals' written descriptions. Appx1208(422:2-423:23); Appx1209(426:12-427:10); Appx2135-2145(claim chart).

## IV. In The Alternative, Appellants Are Entitled To Judgment As A Matter Of Law On Written Description Or Enablement.

Although granting a new trial would be the narrowest grounds to resolve this appeal, this Court can and should fully resolve the case by granting JMOL to Appellants on written description or enablement. *See* Fed. R. Civ. P. 50(a)(1) (JMOL proper where "a reasonable jury would not have a legally sufficient evidentiary basis to find for the party"); *Centocor*, 636 F.3d at 1353 (reversing written description verdict); *Ariad*, 598 F.3d at 1340 (same).

The legal insufficiency of Amgen's asserted claims is clear. Using well-known processes, Amgen isolated two antibodies that bind to a well-known antigen, PCSK9. It then used another well-known technique, x-ray crystallography, to identify the amino acids on PCSK9 where those two antibodies bind. From that, Amgen proceeded to claim *all antibodies* that bind to those same amino acids. Rarely has so much been claimed from so little.

Amgen argues that identifying those amino acids gives it possession of the entire genus of functionally claimed antibodies, and that one can use the binding site information to obtain all of the other antibodies in the genus. But as a matter of science, these contentions are *categorically false*. Knowing where an antibody binds to an antigen tells one *nothing* about the structure of any other antibody; accordingly, the patents fail the written description requirement because it is impossible to demonstrate commonality of structure, and two species are incapable of representing the thousands upon thousands of antibodies encompassed by the broad, diverse genus. Furthermore, to make an antibody claimed by the patents, one must engage in a trial-and-error process of generating and screening antibodies for binding, then perform the difficult and unpredictable task of x-ray crystallography to determine if an isolated antibody binds to the claimed residues; and after all of that, one may still not get a sufficient number of antibodies that enable the full scope of the claims. Accordingly, the patents fail the enablement requirement.

### A. Amgen's Written Description Is Insufficient as a Matter of Law.

As this Court has explained, "[f]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable." *AbbVie*, 759 F.3d at 1301. Amgen contends that it adequately described its functional genus claims because it disclosed either "a representative number of species falling within the scope of the genus" or "structural features common to the members of the genus." *Id.* at 1299. But the scientific principles conceded by Amgen's own experts foreclose those arguments, and no rational jury applying the law could accept them.

Regarding the representative species test, Amgen's experts conceded that the claims at issue cover "many, many antibodies"—indeed, just short of "infinite"—but that the specification discloses only two antibodies known to meet those claims. Appx1322(869:14-16); Appx1325(882:5-8); Appx1339(937:24-938:6). They also conceded that the claims cover many structurally diverse antibodies. Appx1307(808:24-809:12). Amgen points to no case, and Appellants are aware of none, in which two examples were found to be representative of so enormous and variable a genus. Indeed, before this Court, Amgen has already wisely retreated from the argument that two examples would suffice. DE56-1 at 15.

Instead, Amgen contends, "the jury heard compelling evidence that the patent discloses at least two dozen representative species within the scope of the claims." *Id.* But the two dozen is no better than the two. To begin with, Amgen's own experts were unable to say that the 22 additional antibodies described in the specification—which merely "co-bin" with the two known antibodies—were actually within the scope of the claims. *See* p. 16, *supra*. Amgen points to no case in which a court has counted species that only *might* fall within the genus in a representative species analysis. But even if the 22 sort-of species are considered, Amgen's disclosure is still insufficient, because those antibodies are not representative of the structural variability of the broad functional genus. Rather, as Dr. Eck testified, many of the co-binning antibodies have "essentially the same" amino acid sequence as Repatha. Appx1243(558:13-19); *cf. AbbVie*, 759 F.3d at 1300 (holding that *two hundred* antibodies with similar structures are not representative of broad, diverse functional genus). Finally, although the asserted claims cover antibodies of *any* species, the only examples in the patent are examples of *human* antibodies, which underscores the legally insufficient disclosure. *See Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1567-68 (Fed. Cir. 1997) (disclosure of rat cDNA not descriptive of broader invention consisting of mammalian and vertebrate cDNA).

Amgen's evidence on "common structural features" is even weaker. Pressed to identify a single common structural feature, Amgen's experts named none. The best they could muster was Dr. Rees's circular assertion that "my way of thinking of the structural features notion is that … all the antibodies … that bind to this region must share structural features in those antibodies that allow them to get the shape fitting that is required." Appx1332(908:20-24). In other words, the common *structure* is the common *function*, in that all antibodies that bind in the desired way must share whatever degree of structure that allows them to bind in that way. That is simultaneously utterly circular and utterly incompatible with the reality that function and structure are not synonymous. These same circular assertions also do not allow a skilled artisan to "visualize or recognize" the members of the genus, the *sine qua non* of which is to "distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350.

Amgen's struggle to identify common structure underscores the central flaw in its case: its theory that describing part of an antigen (*i.e.*, the claimed residues on PCSK9) describes the antibodies that bind there. That theory simply has no basis in science. It is no more accurate than saying that describing the location of a parking space describes the vehicles that pull into it. As Dr. Eck explained, the surface of PCSK9 is not "somehow a mold that tells us what the structure of the antibody that binds to it in a particular place has to be. It just does not work that way." Appx1414(1111:9-11). As important for JMOL purposes, Amgen's own expert, Dr. Petsko, conceded that Dr. Eck was "right" that describing an antigen does not predict the structure of an antibody. Appx1314(836:9-11). That concession is fatal for Amgen. Without any scientific support for the proposition that describing the binding site discloses the claimed antibodies, Amgen's identification of PCSK9 residues amounts to "a definition of a useful result rather than a definition of what achieves that result," which this Court has held is insufficient to satisfy the written description requirement. *Ariad*, 598 F.3d at 1350; *see Centocor*, 636 F.3d at 1351 (reversing jury verdict and granting JMOL where disclosure amounted to mere "wish list of properties that a[n] … antibody should have," including "the ability to bind in the same place" as a disclosed antibody).

### B. Amgen's Claims Are Invalid as a Matter of Law for Lack of Enablement.

Likewise, Amgen's claims are insufficiently enabled as a matter of law, because the specification does not "teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech*, 108 F.3d at 1365. Amgen contends that a skilled artisan reading the specification can repeat the same steps that Amgen itself took to isolate its antibodies. But not only does that not enable an artisan to produce the "full scope" of Amgen's broadly claimed genus; Amgen's labor-intensive process of screening thousands of antibodies to look for those that bind to certain PCSK9 residues constitutes precisely the kind of "starting point for further iterative research in an unpredictable … field" that requires "undue experimentation" and fails to satisfy the enablement requirement. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013). One wishing to create antibodies encompassed by the claims must repeat the same multi-step, trial-and-error process Amgen undertook (and continues to undertake) until—after weeks, months, or years generating thousands upon thousands of antibodies—he finally generates an antibody that binds to a claim-covered residue and blocks PCSK9 from binding. Appx1387; Appx1393-1403. And even then, one does not know if the antibody binds to residues specified in the claims (thereby actually obtaining what the patent claims) without engaging in the difficult and uncertain process of x-ray crystallography; indeed, some antibodies cannot be crystallized at all. After all that, one may still not get a sufficient number of antibodies that enable the full scope of the claims. *See* pp. 17, 33-34, *supra*. If that is not "undue experimentation," nothing is.

## V. At A Minimum, The Permanent Injunction Order Should Be Vacated.

If the Court affirms the judgment, it should nevertheless vacate the district court's unprecedented and draconian order removing Praluent from the market, for three independent reasons.

### A. Granting an Injunction that Disserves the Public Interest Is Irreconcilable with *eBay* and Basic Principles of Equity.

First, the district court's order is irreconcilable with binding Supreme Court precedent and basic equitable principles. An "injunction is a drastic and extraordinary remedy, which should not be granted as a matter of course." *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 165 (2010). In *eBay*, the Supreme Court displaced this Court's general rule that an injunction automatically follows a finding of patent infringement, explaining that a plaintiff seeking a permanent injunction for patent infringement "*must demonstrate*: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; *and* (4) that the public interest would not be disserved by a permanent injunction." 547 U.S. at 391 (emphases added).

The district court's decision to grant the injunction facially contradicts *eBay*. The court explicitly found that the fourth factor, the public interest, militated *against* an injunction. Appx33-34¶¶10-11. The court explained that "[t]he public generally is better served by having a choice of available treatments," that "taking an independently developed, helpful drug off the market does not benefit the public," and that "the public interest of having a choice of drugs should prevail." Appx33-34¶11. The court nevertheless followed its finding that the "public interest factor weighs in favor of" Appellants with the declaration that Amgen's "motion for a permanent injunction is granted." Appx34¶12.

Commentators immediately recognized the court's decision to take an FDA-approved innovator drug off the market in conceded disservice of the public interest as "nearly unprecedented," "shock[ing]," and "very strange."[12] Indeed. Neither the district court nor Amgen has cited any case after *eBay* in which this Court (or any court, for that matter) has approved an injunction that concededly *disserves* the public interest. And for good reason: the language of *eBay* squarely forbids that result. 547 U.S. at 391. Indeed, even Amgen's proposed injunction order, submitted before the district court's decision, presumed (correctly) that the court must "find[] that the entry of an order of injunction will not disserve the public interest[.]" Appx2317.

The most basic principles of equity (in addition to *eBay*) underscore that an equitable remedy that disserves the public interest may not be granted. After all, an injunction is an equitable and discretionary remedy, and the cardinal command of a court of equity is to "do equity." *Hecht Co. v. Bowles*, 321 U.S. 321, 329

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[12] Matthew Herper, *Could Amgen's Patent Victory Be Bad For Medicine?*, Forbes (Jan. 6, 2017), http://bit.ly/2ioTTmR; *id.* (quoting Prof. Jacob Sherkow); Prof. Rachel Sachs, *Let's All Worry About the Effects of Patent Injunctions Against Drug Manufacturers*, Harvard Law Bill of Health Blog (Jan. 6, 2017), http://bit.ly/2jhLYYM.

(1944). Thus, an injunction that the issuing court itself views as contrary to the public interest should be the null set.

The Supreme Court has emphasized the paramount importance of the public interest in the equitable analysis. *See, e.g.*, *Winter v. NRDC*, 555 U.S. 7, 23 (2008) (finding irreparable injury "outweighed by the public interest"). And the public interest could hardly be clearer than in cases implicating public health. "[F]or good reason, courts have refused to permanently enjoin activities" promoting public health and choice of products. *Cordis Corp. v. Boston Sci. Corp.*, 99 F. App'x 928, 935 (Fed. Cir. 2004) (Appx2458-Appx2459). Indeed, this Court recently dismissed an objection to an injunction favoring Apple because "Apple does not seek to enjoin the sale of lifesaving drugs." *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 647 (Fed. Cir. 2015). Here, however, Amgen seeks precisely that forbidden fruit: "to enjoin the sale of lifesaving drugs." *Id.*

### B. The Injunction Order Is Impermissibly Unreasoned.

The district court's decision ordering Praluent off the market with virtually no explanation itself warrants vacatur. The Supreme Court has vacated injunctions where a district court provided analysis "in only a cursory fashion," *Winter*, 555 U.S. at 26, and this Court has similarly vacated injunctions imposed absent a reasoned explanation, *see ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1339-41 (Fed. Cir. 2012).

Here, the district court provided essentially no reasoning for its far-reaching injunction. The court's discussion of the irreparable harm factor merely described the parties' arguments and then stated, with no explanation, that the factor "weighs in favor of plaintiffs." Appx32¶7. So too on the balance of hardships, which the court found to be "neutral" with zero reasoning. Appx33¶9. The court's discussion of the adequacy of money damages included at best one sentence of reasoning, itself contradicted by the court's later suggestion that the parties might "reach an appropriate business resolution," which presumably would consist of an ongoing royalty—money damages. Appx32¶8,Appx34¶12. Most egregious, following its finding that "[t]he public interest factor weighs in favor of [Appellants]"—the only factor for which the court *did* engage in any meaningful analysis—the court simply announced the *ipse dixit* that "Plaintiffs' motion for a permanent injunction … is granted." Appx34¶12. Granting such extraordinary relief with so little reasoning itself warrants vacatur.

### C. Ordering an Injunction Was an Abuse of Discretion.

Finally, the injunction order is "as inexplicable as it is unexplained," *Felkner v. Jackson*, 562 U.S. 594, 598 (2011), and a paradigmatic abuse of discretion.

On the first *eBay* factor, irreparable harm, Amgen argued that it had suffered reputational damage, harm to its business model, and non-compensable price erosion as a result of Praluent's presence on the market. Appx32¶¶7-8. But as

Appellants' expert testified, and as common sense confirms, it is simply not "credible" for Amgen—a leading pharmaceutical company—to suggest that its reputation for innovation or its business model will suffer irreparably absent an injunction in this case. Appx2440(479:7-9).

Nor did Amgen make a plausible case that money damages were so inadequate as to warrant taking Praluent away from patients. Appx2436(472:13)-Appx2438(478:4). Royalties are the norm in infringement cases like this one, and pharmaceutical companies accusing innovator competitors (as opposed to generic manufacturers) of infringement often decline even to seek an injunction. *See* Sachs, n.12, *supra* (discussing Merck's declining to pursue injunction pulling Gilead's drug off market). Indeed, Amgen concededly "didn't pursue a preliminary injunction." Appx976(10:10-14). If Amgen was willing to accept money damages for two years of district court litigation—including nine months after the jury verdict—its contention that damages are not an appropriate remedy going forward lacks credibility.

The evidence on the balance of hardships was hardly "neutral." Appx33¶9. Appellants presented evidence that a permanent injunction would require them to, *inter alia*, shut down production, lay off employees, lose billions in Praluent-related investments, and endure lasting reputational harm. Appx2385(267:7-22); Appx2388(277:6-14); Appx2392(293:25-294:8). Amgen's chief response was to claim that Appellants launched Praluent "at risk" once they learned of Amgen's patent application in 2009. But Appellants had indisputably begun to develop Praluent long before they knew Amgen was also pursuing Repatha. Appx2411(372:3-6). And the notion that a sophisticated company like Amgen would terminate its own ongoing, billion-dollar development program because of a mere *application* is fanciful.

Finally, and most important, the public interest weighs overwhelmingly against taking Praluent off the market. Not only would an injunction take an FDA-approved, life-saving innovator medicine away from thousands of patients who now rely on it, but it would leave the vast majority of them with no effective alternative, because Repatha does not come in the low-dose version that treats more than 85 percent of Praluent patients. Appx2385(266:3-23); Appx2392(296:3-7); Appx2403(338:12-21); Appx2431(449:2-450:12); Appx2432(455:1-9). Were Praluent withdrawn from the market, those patients would face a choice between taking a larger dose than necessary or discontinuing the therapy entirely. Appx2392(296:9-23); Appx2403(338:18-339:23). Neither of these options is medically sound, yet they are the inevitable result of the deeply misguided injunction here.

## CONCLUSION

The Court should vacate or reverse the judgment below or, at a minimum, vacate the permanent injunction.

Respectfully submitted,

s/Paul D. Clement
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March 3, 2017

## CERTIFICATE OF COMPLIANCE

1. This Brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because, according to the "word count" function of Microsoft Word 2010, the Brief contains 13,975 words, excluding the parts of the Brief exempted from the word count by Rule 32(a)(7)(B)(iii) of the Federal Rules of Appellate Procedure and Federal Circuit Rule 32(b).

2. This Brief complies with the typeface requirements of Rule 32(a)(5) and the typestyle requirements of Rule 32(a)(6) of the Federal Rules of Appellate Procedure because the Brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point Times New Roman font.

Dated: March 3, 2017

s/Paul D. Clement
Paul D. Clement

# ADDENDUM

Final Judgment (Jan. 3, 2017)............................................................................Appx27

Order Granting Motion for Permanent Injunction (Jan. 5, 2017).... Appx28-Appx34

Order Denying Post-Trial Motions (Jan. 3, 2017)..........................................Appx35

Memorandum Opinion (Jan. 3, 2017)............................................. Appx36-Appx64

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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| AMGEN INC., AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC<br><br>Plaintiffs,<br><br>v.<br><br>SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC.,<br><br>Defendants. | ) | Civ. No. 14-1317-SLR<br>(Consolidated) |

**FINAL JUDGMENT FOLLOWING POST TRIAL MOTION PRACTICE PURSUANT TO FED. R. CIV. P. 54(b)**

For reasons stated in the court's memorandum opinion and order of January 3, 2017;

IT IS ORDERED AND ADJUDGED that judgment be and is hereby entered in favor of plaintiffs Amgen, Inc., Amgen Manufacturing, Limited and Amgen USA Inc. and against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc.

United States District Judge

Dated: 1/3/2017

(By) Deputy Clerk

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

| | | |
|---|---|---|
| AMGEN INC., AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC<br><br>Plaintiffs,<br><br>v.<br><br>SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC.,<br><br>Defendants. | ) | Civ. No. 14-1317-SLR<br>(Consolidated) |

**MEMORANDUM ORDER**

At Wilmington this 5th day of January, 2017, having reviewed the papers filed in connection with plaintiffs' motion for permanent injunction, and having heard oral argument on the same;

IT IS ORDERED that the motion (D.I. 336) is granted, for the following reasons:

1. **Procedural background.**[1] On October 17, 2014, plaintiffs Amgen Inc., Amgen Manufacturing Limited, and Amgen USA Inc. (collectively "plaintiffs") brought this action alleging infringement of certain patents against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively "defendants"). (D.I. 1) On February 22, 2016, defendants stipulated to infringement of certain asserted claims of the patents-in-suit. (D.I. 235) The parties proceeded to trial

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[1] A fuller recitation of the procedural and factual background may be found in the court's post-trial opinion. (D.I. 389)

on March 8, 2016, arguing the validity of the asserted claims. On March 16, 2016, the jury returned a verdict finding the asserted claims of the patents-in-suit valid. (D.I. 302, 304) On March 23 and 24, 2016, the court heard evidence on plaintiffs' request for a permanent injunction. The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a).

2. **Factual background.**[2] Physicians recognize dyslipidemia caused by elevated LDL ("low density lipoprotein" or "bad" cholesterol) as a major risk factor for cardiovascular disease. Starting in 2005, plaintiffs developed Repatha™ ("Repatha"), which uses the active ingredient "evolocumab." Evolocumab is a monoclonal antibody that targets PCSK9[3] to prevent it from engaging the low density lipoprotein receptor ("LDLR") protein and ultimately lowers the levels of LDL in the blood. Plaintiffs filed for FDA approval on August 27, 2014, which they received in August 2015. Plaintiffs then launched Repatha. Repatha is offered in a 140 mg dose and 420 mg dose.

3. Defendants developed PRALUENT® alirocumab ("Praluent"), a monoclonal antibody that reduces LDL cholesterol levels in the blood. Defendants filed for regulatory approval in November 2014 using an orphan drug priority review voucher, and received FDA approval in July 2015. Defendants then launched Praluent, which is provided in a 75 mg low dose and a 150 mg high dose. According to defendants, more than 80% of patients on Praluent are able to hit their LDL target on the low dose.

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[2] The facts and arguments discussed below are taken from the parties' briefing and corresponding hearing transcripts. (D.I. 347, 348, 362, 369, 376)

[3] Proprotein convertase subtilisin kexin type 9 is a specific antibody involved in regulating the levels of the low density lipoprotein receptor protein.

4. **Standard.** In *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006) (vacating and remanding *MercExchange, L.L.C. v. eBay Inc.*, 401 F.3d 1323, 1339 (Fed. Cir. 2005)) (hereinafter "*eBay*"), the Supreme Court overruled the Federal Circuit's longstanding "general rule that courts will issue permanent injunctions against patent infringement absent exceptional circumstances." The Supreme Court held in *eBay* that permanent injunctions in patent cases must be based on a case-by-case assessment of the traditional equitable factors governing injunctions. *Id.* at 391-92. That is, to be awarded a permanent injunction, a plaintiff must demonstrate: "(1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *Id.* at 391. "[T]he decision whether to grant or deny injunctive relief rests within the equitable discretion of the district courts, and that discretion must be exercised consistent with traditional principles of equity, in patent disputes no less than in other cases governed by such standards." *Id.* at 394.

5. In *eBay*, the Court specifically cautioned against the application of categorical rules, classifications, and assumptions in these analyses. *Id.* at 392. Nevertheless, courts (presumably struggling to balance the absence of a presumption of irreparable harm with a patentee's right to exclude) have frequently focused upon the nature of the competition between a plaintiff and a defendant in the relevant market in the context of evaluating irreparable harm and the adequacy of money damages. *See, e.g., TruePosition Inc. v. Andrew Corp.*, 568 F. Supp. 2d 500, 531 (D. Del. 2008). Courts

awarding permanent injunctions typically do so under circumstances in which the plaintiff practices its invention and is a direct market competitor.[4] Plaintiffs also frequently succeed when their patented technology is at the core of their business, and/or where the market for the patented technology is volatile or still developing.[5]

6. There is no dispute that both Repatha and Praluent are approved by the FDA to lower LDL cholesterol in a select group of patients. They are the only therapeutics in the PCSK9 inhibitor market, making the parties head-to-head competitors in a targeted and developing market. The parties at bar are large companies with multiple products, both on the market and in the development pipeline. The parties are also each innovators, having independently developed their PCSK9 inhibitor.

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[4] *See, e.g., Muniauction, Inc. v. Thomson Corp.*, 502 F. Supp. 2d 477, 482 (W.D. Pa. 2007) ("Plaintiff and defendants are direct competitors in a two-supplier market. If plaintiff cannot prevent its only competitor's continued infringement of its patent, the patent is of little value.") (granting permanent injunction); *Johns Hopkins Univ. v. Datascope Corp.*, 513 F. Supp. 2d 578, 586 (D. Md. 2007) (granting permanent injunction where infringing product was plaintiffs' "only competition" and "thus, its sale reduce[d] the [p]laintiffs' market share"); *Transocean Offshore Deepwater Drilling, Inc. v. GlobalSantaFe Corp.*, 2006 WL 3813778, *4 (S.D. Tex. Dec. 27, 2006) (granting permanent injunction requiring structural modifications to infringing deepwater drilling rigs where "the customer base for deep water drill rigs is small, and [defendant] has not only used [its] rigs equipped with the infringing structure to compete for the same customers and contracts as [plaintiff], but also to win contracts over competing bids from [plaintiff]").

[5] *See, e.g., Martek Biosciences Corp. v. Nutrinova Inc.*, 520 F. Supp. 2d 537, 558-59 (D. Del. 2007) (granting permanent injunction where plaintiff was a direct competitor "likely to lose market share that it may not be able to recapture," as plaintiff's patented technology was its primary revenue source, and defendant was plaintiff's only competitor and was "targeting [plaintiffs] customers in that industry"); *TiVo, Inc. v. EchoStar*, 446 F. Supp. 2d 664 (E.D. Tex. 2006) (granting permanent injunction where: (1) parties were direct competitors; (2) "plaintiff [was] losing market share at a critical time in the market's development;" (3) the parties agreed that customers in the relevant market tend to remain customers of the company they first purchased from; and (4) as a "relatively new company with only one primary product," plaintiff's "primary focus is on growing a customer base specifically around the product" competing with the infringing product).

7. **Irreparable harm.** Plaintiffs present traditional evidence of loss of market share and momentum. Specifically, plaintiffs allege that they have been forced to compete with defendants for contracts with insurers and exclusive formulary positions, particularly since defendants were first to market. Plaintiffs argue that defendants' market position is causing harm to their reputation as the innovator in the PCSK9 cholesterol-lowering medicine, and defendants' marketing of Praluent as "The First U.S. FDA-Approved PCSK9 Inhibitor" compounds such harm. Defendants respond that it is well known that plaintiffs were the first to file a biologics license application with the FDA and receive regulatory approval worldwide for Repatha. According to defendants, Repatha would have faced pricing pressures even without competition from Praluent. This factor weighs in favor of plaintiffs.

8. **Remedies at law.** Plaintiffs assert that patent protection is fundamental to their business model and they will not be able to fully recoup their investment in Repatha without an injunction. Monetary damages will not suffice under the present circumstances, as plaintiffs intended to use their patent to maintain market exclusivity. Moreover, the developing PCSK9 inhibitor market, together with the reputational harm, make monetary damages speculative. In contrast, defendants allege that plaintiffs have not suffered reputational harm and, even if they did, such harm is measurable. Defendants maintain that monetary damages are sufficient, in as much as the parties' experts quantified the extent of past financial injury during the liability phase of the case. This quantification, however, does not include reputational harm and defendants do not offer any method of calculation. This factor weighs in favor of plaintiffs.

Case: 17-1480 Document: 105 Page: 86 Filed: 03/07/2017

9. **Balance of hardships.** Both parties have spent billions of dollars and over a decade of work to bring their respective products to market. If an injunction does not issue, plaintiffs lose the market share occupied by defendants and face continued competition. If an injunction issues, defendants lose business going forward and the ability to make and market Praluent. This factor is neutral.

10. **Public interest.** Plaintiffs rely on the traditional notions of being a patent holder and a verdict winner. Plaintiffs point to the FDA's approval of Repatha to treat all patients covered by the Praluent label to assuage the consequence of an injunction on patients. (JTX 392) Defendants rely heavily on the availability of (and physicians' alleged preference for) the low 75 mg dose of Praluent to argue that an injunction would harm the treatment of patients. Defendants also point to Praluent's label stating that "[t]he recommended starting does for Praluent is 75 mg." (PTX 5012)

11. The court will not substitute its judgment for that of the FDA, nor delve into weighing testimony on the propriety of treating patients with the 75 mg dose of Praluent (instead of the 150 mg dose or the 140 mg dose of Repatha). The public generally is better served by having a choice of available treatments. Therefore, the court finds itself between a rock and a hard place, i.e., being a patent holder and a verdict winner should be a meaningful factor in the balancing test, but taking an independently developed, helpful drug off the market does not benefit the public. "[T]he touchstone of the public interest factor is whether an injunction, both in scope and effect, strikes a workable balance between protecting the patentee's rights and protecting the public from the injunction's adverse effects." *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 863 (Fed. Cir. 2010), aff'd, 564 U.S. 91 (2011). The court concludes that the public

interest of having a choice of drugs should prevail. This factor weighs in favor of defendants.

12. **Conclusion.** For the aforementioned reasons, plaintiffs have demonstrated irreparable harm, as well as the inadequacy of money damages. The public interest factor weighs in favor of defendants. Plaintiffs' motion for a permanent injunction (D.I. 336) is granted. Given the ramifications of an injunction, the court will delay its imposition for thirty (30) days to allow defendants the opportunity to appeal and request expedited review of this ruling by the Federal Circuit, and/or to encourage the parties to reach an appropriate business resolution.

United States District Judge

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

| | | |
|---|---|---|
| AMGEN INC., AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC<br><br>Plaintiffs,<br><br>v.<br><br>SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC.,<br><br>Defendants. | ) | Civ. No. 14-1317-SLR<br>(Consolidated) |

**O R D E R**

At Wilmington this 3rd day of January 2017, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Defendants' renewed motion for judgment as a matter of law on written description and enablement (D.I. 332) is denied.

2. Defendants' motion for a new trial (D.I. 331) is denied.

3. Plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338) is denied as moot.

United States District Judge

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC

Plaintiffs,

v.

SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC.,

Defendants.

Civ. No. 14-1317-SLR
(Consolidated)

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**MEMORANDUM OPINION**

Dated: January 3, 2017
Wilmington, Delaware

ROBINSON, District Judge

## I. INTRODUCTION

On October 17, 2014, plaintiffs Amgen Inc., Amgen Manufacturing Limited, and Amgen USA Inc. (collectively "plaintiffs") brought this action alleging infringement of U.S. Patent Nos. 8,563,698; 8,829,165 ("the '165 patent"); and 8,859,741 ("the '741 patent") against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively "defendants"). (D.I. 1) Plaintiffs filed an amended complaint on November 17, 2014. (D.I. 10) Defendants answered the complaint on December 15, 2014. (D.I. 18, 19, 20) The court held a *Markman* hearing on September 17, 2015, and issued a claim construction order on October 25, 2015 construing certain disputed limitations of the '165 and '741 patents. (D.I. 151) On January 29, 2016, the court granted plaintiffs' motion to amend the complaint, which amended complaint was filed the same day consolidating into a single complaint plaintiffs' pleadings from four lawsuits (resulting in the addition of U.S. Patent Nos. 8,871,913; 8,871,914; 8,883,983; and 8,889,834). (D.I. 183, 184) Defendants answered the amended complaint on February 16, 2016. (D.I. 220) On February 22, 2016, defendants stipulated to infringement of the asserted claims of the patents-in-suit.[1] (D.I. 235) The court held a final pretrial conference on February 22, 2016.

The parties proceeded to trial on March 8, 2016, arguing the validity of the asserted claims. The court decided a series of evidentiary issues and *Daubert* motions before and during trial. (D.I. 226, 249, 250, 264, 269, 280) On March 16, 2016, the court granted defendants' judgment as a matter of law regarding willful infringement.

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[1] Claims 2, 7, 9, 15, 19, and 29 of the '165 patent and claim 7 of the '741 patent.

(D.I. 302) On March 16, 2016, the jury returned a verdict finding the asserted claims of the patents-in-suit valid. (D.I. 304) Presently before the court are defendants' motions for a new trial and judgment as a matter of law on written description and enablement (D.I. 331, 332), and plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338). The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a).

## II. BACKGROUND

### A. Parties

Amgen Inc. and Amgen USA Inc. are corporations organized under the laws of the State of Delaware, with a principal place of business in Thousand Oaks, California. Amgen Manufacturing, Limited is a corporation organized under the laws of Bermuda with its principal place of business in Juncos, Puerto Rico. Sanofi is a company organized under the laws of France with its principal headquarters in Paris, France. Sanofi-Aventis U.S. LLC is a company organized under the laws of the State of Delaware with its principal place of business in Bridgewater, New Jersey. Aventisub LLC is a company organized under the laws of the State of Delaware having its principal place of business in Greenville, Delaware.[2] Regeneron Pharmaceuticals, Inc. is a corporation organized under the laws of the State of New York with its principal place of business in Tarrytown, New York. (D.I. 184 at ¶¶ 2-8, 12)

### B. Technology

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[2] Aventisub is the surviving entity from a June 2014 merger involving Aventis Pharmaceuticals Inc. and has assumed the assets, liabilities, and/or responsibilities of Aventis Pharmaceuticals Inc. Aventis Pharmaceuticals Inc. was a Delaware corporation having a principal place of business in Bridgewater, New Jersey.

Case: 17-1480 Document: 39 Page: 92 Filed: 05/09/2017

### 1. The patents-at-issue

The '165 patent issued on September 9, 2014 and the '741 patent issued on October 14, 2014 (collectively "the patents-at-issue"). (JTX 2, 3) The patents-at-issue are titled "Antigen binding proteins to proprotein convertase subtilisin kexin type 9 (PCSK9)" and share a specification.[3] Proprotein convertase subtilisin kexin type 9 ("PCSK9") is a specific antibody involved in regulating the levels of the low density lipoprotein receptor ("LDLR") protein. (1:57-59) Monoclonal antibodies have a known "Y-shaped" structure made up of "two identical pairs of polypeptide chains," each pair having a heavy chain and a light chain. The carboxy-terminal portion of each chain typically defines a constant region. "The amino-terminal portion of each chain typically includes a variable region of about 100 to 110 or more amino acids that typically is responsible for antigen recognition." This allows different antibodies to bind to different antigens. (33:1-27) The specification describes monoclonal antibodies that bind to a specific region of PCSK9. (3:5-6)

The specification provides that 3000 human monoclonal antibodies were "rescreened for binding to wild-type PCSK9 to confirm stable hybridomas were established," and "a total of 2441 positives repeated in the second screen." (78:4-6, 35) Of these, "384 antibodies . . . blocked the interaction between PCSK9 and the LDLR well [and] 100 antibodies blocked the interaction strongly," "inhibit[ing] the binding interaction of PCSK9 and LDLR [at] greater than 90%." (80:22-26) The "screen of the 384 member subset identified 85 antibodies that blocked interaction between the PCSK9 mutant enzyme and the LDLR [at] greater than 90%." (80:35-37) The specification provides the amino acid sequence of over two dozen of the identified antibodies. (Figures 2A-2D, 3A-3JJ, 15A-15D, 17:60-18:3, 20:1-8, 85:7-43) The specification describes the use of "epitope binning assays"[4] to characterize the different epitopes on PCSK9. 21B12 and 31H4 are representative members of two epitope bins that do not compete with each other for binding to PCSK9. (88:34-89:19) X-ray crystallography experiments were used to characterize the 21B12 and 31H4 binding sites. (99:56-103:60)

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[3] All references are to the '165 patent unless otherwise indicated.

The claims reference specific amino acids at designated positions in SEQ ID NO: 1 and/or 3, which are specific amino acid sequences of PCSK9. (124-133) Claim 1 of the '165 patent recites:

> An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

(427:47-52) Claim 1 of the '741 patent recites:

> An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

('741 patent, 427:36-40) At trial, defendants argued that the asserted claims were invalid for lack of written description and enablement and were obvious in light of the prior art.

**2. Repatha™ and PRALUENT®**

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[4] Epitope binning assays are used to determine the ability of an antibody to block another's binding to the antigen. Antibodies with similar blocking profiles are grouped into a bin, indicating these antibodies bind to the same or overlapping epitopes. (88:34-89:37; D.I. 344 at 799:7-800:16)

Physicians recognize dyslipidemia caused by elevated LDL ("low density lipoprotein" or "bad" cholesterol) as a major risk factor for cardiovascular disease. Plaintiffs developed Repatha™ ("Repatha"), which uses an active ingredient "evolocumab" (identified as "21B12" in the specification). As described in the specification, evolocumab is a monoclonal antibody that targets PCSK9 to prevent it from engaging LDLR and ultimately lowers the levels of LDL in the blood. The FDA approved Repatha in August 2015. (D.I. 184; D.I. 342 at 241:15-24; D.I. 362 at 5) Defendants developed PRALUENT® alirocumab ("Praluent"), a monoclonal antibody that reduces LDL cholesterol levels in the blood. The FDA approved Praluent in July 2015. (D.I. 342 at 347:6-9, 350:23-351:5; D.I. 362 at 5)

## III. STANDARDS OF REVIEW

### A. Renewed Motion for Judgment as a Matter of Law

The Federal Circuit "review[s] a district court's denial of judgment as a matter of law under the law of the regional circuit. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1325 (Fed. Cir. 2016) (citation omitted). In the Third Circuit, a "court may grant a judgment as a matter of law contrary to the verdict only if 'the record is critically deficient of the minimum quantum of evidence' to sustain the verdict." *Acumed LLC v. Advanced Surgical Servs., Inc.*, 561 F.3d 199, 211 (3d Cir. 2009) (citing *Gomez v. Allegheny Health Servs., Inc.*, 71 F.3d 1079, 1083 (3d Cir. 1995)); *see also McKenna v. City of Philadelphia*, 649 F.3d 171, 176 (3d Cir. 2011). The court should grant judgment as a matter of law "sparingly," and "only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability." *Marra v.*

*Philadelphia Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007) (citing *Moyer v. United Dominion Indus., Inc.*, 473 F.3d 532, 545 n.8 (3d Cir. 2007)). "In performing this narrow inquiry, [the court] must refrain from weighing the evidence, determining the credibility of witnesses, or substituting [its] own version of the facts for that of the jury. *Id.* (citing *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)). Judgment as a matter of law may be appropriate when there is "a purely legal basis" for reversal "that does not depend on rejecting the jury's findings on the evidence at trial." *Acumed*, 561 F.3d at 211.

**B. Motion for a New Trial**

Federal Rule of Civil Procedure 59(a) provides, in pertinent part:

> A new trial may be granted to all or any of the parties and on all or part of the issues in an action in which there has been a trial by jury, for any of the reasons for which new trials have heretofore been granted in actions at law in the courts of the United States.

Fed. R. Civ. P. 59(a). The decision to grant or deny a new trial is within the sound discretion of the trial court and, unlike the standard for determining judgment as a matter of law, the court need not view the evidence in the light most favorable to the verdict winner. *See Allied Chem. Corp. v. Daiflon, Inc.*, 449 U.S. 33, 36 (1980); *Leonard v. Stemtech Int'l Inc*, 834 F.3d 376, 386 (3d Cir. 2016) (citing *Olefins Trading, Inc. v. Han Yang Chem. Corp.*, 9 F.3d 282 (3d Cir. 1993)); *LifeScan Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 345, 350 (D. Del. 2000) (citations omitted); *see also* 9A Wright & Miller, *Federal Practice and Procedure* § 2531 (2d ed. 1994) ("On a motion for new trial the court may consider the credibility of witnesses and the weight of the evidence."). Among the most common reasons for granting a new trial are: (1) the jury's verdict is against the clear weight of the evidence, and a new trial must be granted to prevent a

Case: 17-1480 Document: 105 Page: 96 Filed: 08/29/2017

miscarriage of justice; (2) newly-discovered evidence exists that would likely alter the outcome of the trial; (3) improper conduct by an attorney or the court unfairly influenced the verdict; or (4) the jury's verdict was facially inconsistent. *See Zarow–Smith v. N.J. Transit Rail Operations*, 953 F. Supp. 581, 584-85 (D.N.J. 1997) (citations omitted). The court must proceed cautiously, mindful that it should not simply substitute its own judgment of the facts and the credibility of the witnesses for those of the jury. Rather, the court should grant a new trial "only when the great weight of the evidence cuts against the verdict and a miscarriage of justice would result if the verdict were to stand." *Leonard*, 834 F.3d at 386 (citing *Springer v. Henry*, 435 F.3d 268, 274 (3d Cir. 2006) and *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1352-53 (3d Cir. 1991)) (internal quotation marks omitted).

## IV. MOTION FOR JMOL

### A. Procedural Issue

Defendants renew their motion for JMOL on the issue of lack of written description and enablement, arguing that the evidence presented at trial was legally sufficient to show that the specification lacked written description and was not enabled. Plaintiffs challenge the propriety of the renewed motion as defendants did not formally move for JMOL under Rule 50(a) during trial. Fed. R. Civ. P. 50(a).

Rule 50(a) requires the movant to "specify the judgment sought and the law and facts that entitle the movant to judgment." Fed. R. Civ. P. 50(a). "The purpose of th[is] requirement is to afford the opposing party an opportunity to cure the defects in proof that might otherwise preclude the party from taking the case to the jury." *See Duro–Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1105 (Fed. Cir. 2003). The caselaw indicates that a Rule 50(b) JMOL motion is properly founded where an oral Rule 50(a) motion was lodged; or a mere technical failure to comply with Rule 50(a) occurred, i.e., "the party clearly challenged the sufficiency of the evidence on the disputed issue at some point during trial, thereby alerting the opposing party as to the grounds on which the evidence is allegedly insufficient." *Id.* at 1106. The level of specificity required to give the opposing party notice has been the subject of interpretation, and may vary depending on the circumstances of the case. *See Fresenius Medical Care Holdings, Inc. v. Baxter Intern., Inc.*, 2007 WL 518804, *5 (N.D. Cal. Feb. 13, 2007) (collecting Federal Circuit authority).

At the close of defendants' case, on March 10, 2016, the court indicated that the parties should move on to the rest of the case postponing any motion practice until the jury was excused. (D.I. 343 at 720:17-19) After resolving an evidentiary issue outside the presence of the jury, the court stated that "if [plaintiffs] want to do [their] placeholder motion, [plaintiffs] should just say [that they] make a motion, and I will reserve judgment. No need to do much more than that." Plaintiffs moved for JMOL arguing that defendants did not present a sufficient evidentiary basis for a reasonable juror to find for defendants with respect to their invalidity defenses of obviousness, lack of written description, and enablement relating to the . . . asserted claims of the patents-in-suit." The court reserved judgment, and stated that there was "[n]o need for defendants to even respond" to plaintiffs' motion. (D.I. 343 at 725:15-726:8) On March 14, 2016, after further discussion with counsel, the court granted plaintiffs' motion for JMOL on obviousness. (D.I. 345 at 1076:21-1077:6) With this grant, the court issued a short instruction to the jury to explain why the testimony of plaintiffs' expert was cut off. (*Id.* at

1110:9-17) Plaintiffs then rested their case. Defendants did not formally move for JMOL on the issues of written description and invalidity and moved on to their rebuttal case. (*Id.* at 1100:18-23)

"The district court [is] in the best position to judge the sufficiency of [a] Rule 50(a) motion in the context of the trial . . . ." *Gaus v. Conair Corp.*, 363 F.3d 1284, 1287 (Fed. Cir. 2004). Throughout the trial, the crux of the invalidity dispute was defendants' contention of lack of written description and invalidity. Indeed, only these issues went to the jury (defendants having stipulated to infringement and the court having resolved the issue of willful infringement and obviousness). Under the circumstances, the court concludes that plaintiffs were apprised during trial of defendants' allegations of insufficient evidence of written description and enablement, therefore, defendants may proceed with the renewed JMOL.[5]

**B. Standard**

The statutory basis for the enablement and written description requirements, 35 U.S.C. § 112, provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

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[5] In contrast, in *TruePosition Inc. v. Andrew Corp.*, 568 F. Supp. 2d 500 (D. Del. 2008) (cited by plaintiffs), the court found that defendant's pre-verdict JMOL motions regarding infringement (no offer for sale and failure of proof on claims 1 and 22) and damages, together with its counsel's statements, were insufficient to support the post-trial renewed JMOL motion on several other claims (willfulness; no lost profits damages based on the existence of non-infringing alternatives; government use; fraud; and promissory estoppel)).

35 U.S.C. § 112 ¶1. "The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The specification need not teach what is well known in the art. *Id.* (citing *Hybritech v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986)). A reasonable amount of experimentation may be required, so long as such experimentation is not "undue." *ALZA Corp. v. Andrx Pharmaceuticals, Inc.*, 603 F.3d 935, 940 (Fed. Cir. 2010).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). The Federal Circuit has identified several factors that may be utilized in determining whether a disclosure would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. These factors are sometimes referred to as the "*Wands* factors." A court need not consider every one of the *Wands* factors in its analysis, rather, a court is only required to consider those factors relevant to the facts of the case. *See Streck, Inc.*, 655 F.3d at 1288 (citing *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)).

The enablement requirement is a question of law based on underlying factual inquiries. *See Green Edge Enterprises, LLC v. Rubber Mulch Etc., LLC*, 620 F.3d 1287, 1298-99 (Fed. Cir. 2010) (citation omitted); *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1323 (Fed. Cir. 2009) (citation omitted). The burden is on one challenging validity to show, by clear and convincing evidence, that the specification is not enabling. *See Streck, Inc.*, 665 F.3d at 1288 (citation omitted).

A patent must also contain a written description of the invention. 35 U.S.C. § 112, ¶ 1. The written description requirement is separate and distinct from the enablement requirement. *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2011). It ensures that "the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005). The Federal Circuit has stated that the relevant inquiry – "possession as shown in the disclosure" – is an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351.

This inquiry is a question of fact; "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citation omitted). In this regard, defendant must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008) (citation omitted).

**C. Evidence**

**1. 21B12 and 31H4**

The parties agreed that the patent described the screening of about 3,000 antibodies to determine which ones block the binding of PCSK9 to the LDL receptor. The inventors chose 384 antibodies, which blocked PCSK9 "well" for further testing. Of these, 100 antibodies were identified that blocked PCSK9 at over 90%. (D.I. 342 at 283; D.I. 343 at 637:18-639:3, 742) The parties also agreed that the patents-in-suit disclose two antibodies (21B12 and 31H4) that bind to a specific region (the "binding region") of PCSK9.[6] The inventors identified the binding region using X-ray crystallography of 21B12 and 31H4. (D.I. 342 at 283-286:11, 411:4-9, 415:15-21; D.I. 343 at 550:7-17; D.I. 344 at 881:19-882:4, 916:6-8) The specification only provides X-ray crystallography data for 21B12 and 31H4. (D.I. 342 at 283:10-14; D.I. 343 at 645:4-13; D.I. 344 at 882:5-8, 937:24-938:6)

**2. Defendants' evidence**

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[6] The court will refer to this region as "the binding region," rather than the list of names used by the various witnesses including, but not limited to: region, zone, hot zone, central patch, patch, specific area, and sweet spot.

Defendants' expert, Dr. Michael Eck ("Dr. Eck"), testified that the patent disclosed the topography of PCSK9 and the fifteen residue binding region, as well as the crystal structure. (D.I. 343 at 562:19-563:4, 579:1-11; *see also* D.I. 344 at 633:22-634:22, 676:2-677:10) He explained that 21B12 and 31H4 "bind to very defined spots on the surface of PCSK9, [21B12] on one spot, sort of at the edge . . . of the [binding] region [and] 31H4 on the opposite edge." (D.I. 343 at 540:9-541:2; D.I. 345 at 1114:5-1116:13) He stated that 21B12 "probably interacts with probably eighteen amino acids on the surface," four of which are in the binding region. 31H4 interacts with about thirty amino acids total and three in the binding region. (D.I. 343 at 556-557) There are residues in the "middle" of the binding region that are not bound by either 21B12 or 31H4. (D.I. 343 at 546:4-19, 556:4-557:4; D.I. 345 at 1115:10-13) He opined that there are "many different positions on the surface of PCSK9, including this region in the middle, where one would expect antibodies to [be] able to bind, and we see here in [plaintiffs'] patent exactly two examples of antibodies that we know bind in this general vicinity, both on the edge." (D.I. 343 at 541:3-10) There is no example of an antibody "that interacts with the middle and binds [S]153 or likewise D238 or I369 or V380." (D.I. 345 at 1118:14-1119:12) Defendants' other expert, Dr. Donald Siegel ("Dr. Siegel"), similarly concluded that the patents-in-suit do not show the structure of an antibody that binds centrally to the binding region and opined that such an antibody "would have to have a different amino acid sequence or structure than either" 21B12 or 31H4. Moreover, it "would be interacting in a different way." (D.I. 343 at 634:6-25, 645:14-24)

Dr. Eck further explained that there are other possible antibodies, which would have different structures and mechanisms of binding with the binding region. Such antibodies "[m]ight interact with many of the same residues on PCSK9, but [also with] a few different residues." That a certain antibody binds to a particular amino acid on PCSK9 "does not tell you anything at all about the structure," "only about its function." Moreover, there are no developed methods for working back from a binding target "to reliably predict how to make an antibody to bind there." (*Id.* at 547:18-549:16, 564:14-17) Nor can one predict where an antibody would bind on PCSK9 from its structure. (*Id.* at 558:6-9, *see also* 684:3-18) For example, one would expect that "many antibodies with very different chemical structures could bind to PCSK9 and" bind to "D238, but do it in very different ways, with many different antibody structures." (D.I. 343 at 580:11-22, 587:20-588:3, 588:18-590:5)

Dr. Eck testified that the specification disclosed eleven other antibodies that have essentially the same sequence as 21B12. He opined that if the multiple copies of 21B12 are "binding at all, they have to be binding right where [21B12] is." (D.I. 343 at 558:12-559:1) Dr. Eck also testified that there are "on the order of thousands of different versions of . . . 21B12," and the patent does not describe any "examples of antibodies that bind centrally across the middle" of the binding region. (D.I. 345 at 1112:24-1113:19) Dr. Eck briefly described that an antibody may "contact" an amino acid without binding to the amino acid, such that 21B12 contacts the middle amino acid of the EGF-A region (the region of the LDL receptor that binds and interacts with PCSK9). (D.I. 343 at 557, 565:1-18)

Yet another of defendants' experts, Dr. Jeffrey Ravetch ("Dr. Ravetch"), testified that the antibody technology was extremely well developed and a "mature technology." The use of "transgenic mice and phage display," as well as other laboratory methods, were routine techniques. (D.I. 342 at 409:7-11, 413:3-20, 414-415) Dr. Siegel explained that the asserted claims were not limited to human antibodies, but could be mouse or camel antibodies. The structures of such non-human antibodies would be "much different" than human antibodies. (D.I. 343 at 632:20-633:12) He also explained that the asserted claims (excepting claim 29 of the '165 patent) do not specify a particular level of blocking, such that "any small amount of blocking would define an antibody that fit in the genus of antibodies." (*Id.* at 632:15-19)

Dr. Eck explained that to determine similarities of antibodies, a person of ordinary skill considers "their chemical structure, their composition, their primary amino acid sequence and their three-dimensional structure." (*Id.* at 577:21-578:4) He concluded that there are "many antibodies that will meet [the asserted] claims that have nevertheless very diverse and different three-dimensional structures and primary amino acid sequences." He could not "visualize or recognize" these based on the teachings of the specification. Further, "having the expectation that there are many antibodies that will bind [to the binding region] is different than being able to know precisely what those structures are and to be able to realize and make and use any of those structures." (*Id.* at 583:13-584:14) The specification does not offer "clear evidence" of antibodies binding to the "many ways one could have antibodies binding, covering this central region, as well, for example, as binding to the north edge, or binding to the south edge." (D.I. 345 at 1117:2-21)

Dr. Siegel explained that the claims of the patents-in-suit "are very broad" and "cover a large number of antibody structures, not limited in any way." He opined that the specification does not "provide a description of [the] invention." (D.I. 343 at 612:9-

17) Moreover, the claims reciting an antibody that binds to at least one residue (for example D238), do not provide information about the structure or sequence of such antibody. (*Id.* at 630:9-12) He testified that there are no "common structural features . . . described that would make one understand . . . the structures of other antibodies." (*Id.* at 659:3-22) Dr. Siegel concluded that the two antibodies are not representative of antibodies that would bind in the middle of the binding region. (*Id.* at 650:24-651:10) He also opined that the 20 or more sequences reported in the specification are insufficient to represent the diversity of antibodies covered by the asserted claims. (*Id.* at 707:18-22)

As to the enablement requirement, Dr. Siegel testified that it would not be possible to start with the amino acid sequences listed in the specification and make "the full diversity of antibodies that are covered by the claims," because "[i]t's a very unpredictable process" and would require trial and error. (*Id.* at 662:19-663:10) He stated that the methods were known (*id.* at 664-668:9) but, in his opinion, the process would involve undue experimentation, as "there are a lot of steps involved" and there is nothing in the specification to help a researcher "hone in on an antibody that satisfies the claims." (*Id.* at 668:10-669:13) The specification has not disclosed a "quick way of doing" the research, or "taught . . . anything special." (*Id.* at 701:4-8) That the binding region is known is not useful in making the antibodies, as the antibodies must be made and tested to determine where they bind. (*Id.* at 672:22-673:20, 714:10-12) He stated that "even today, we're talking about how immature the art is where you can't take an antigen and figure out how to make an antibody that will bind to it." (*Id.* at 695:5-9)

**3. Plaintiffs' evidence**

Plaintiffs' scientific director, Dr. Simon Jackson ("Dr. Jackson"), testified that the crystallography data "showed . . . the specific amino acids that were . . . binding" and "that the antibodies were binding in a small region side by side on PCSK9." (D.I. 342 at 285) Plaintiffs' expert, Dr. Gregory Petsko ("Dr. Petsko"), testified that when the antibodies bind, they cover "a footprint." (D.I. 344 at 799) Dr. Petsko disagreed with the characterization of 21B12 and 31H4 as "edge binders." He described the antibodies as "very large objects" with "a pretty big footprint on the" binding region, that "don't really hang onto the edge at all." (*Id.* at 805) He explained that the 15 residues that constitute the binding region are covered "virtually perfectly, including . . . [F]379" by 21B12 and 31H4. (*Id.* at 806) On cross-examination, Dr. Petsko was asked: "Based on the information available in the patent as of January 9, 2008, one cannot determine that any of the antibodies disclosed bind to PCSK9 in between where 21B12 and 31H4 bind; is that correct?" He explained that "when a scientist hears the word 'determined,' a scientist often thinks about doing experiments." He responded that without experiments, however, he didn't "know for sure that there are any such antibodies." (*Id.* at 862:19-863:15)

Dr. Petsko testified that example 11 in the patent describes the blocking data for the antibodies, i.e., the ability of the antibody to prevent the LDL receptor from binding to PCSK9. Example 3 of the patent discloses that the inventors were in possession of 85 antibodies that blocked at more than 90%. He explained that the 384 member subset blocked quite reasonably. (*Id.* at 796-797) Dr. Jackson explained that "[b]inning is a way to group antibodies . . . depending on how they bind and where they bind to the protein, in this case PCSK9." (D.I. 342 at 267) Antibodies that co-bin cannot bind "at the same time," instead they "compete against each other for binding to the site." (*Id.* at 269) The specification uses 21B12 as a representative antibody for bin 1 and 31BH4 for bin 3. (D.I. 344 at 270) Dr. Petsko testified that "binning experiments . . . tell you whether antibodies have overlapping footprints on the surface of PCSK9." (*Id.* at 798:15-17) He explained that bin 1 (containing seventeen antibodies) and bin 3 (containing seven antibodies) "represent the collection of antibodies that co-bin with 21B12 and the collection that co-bin with 31H4," respectively.[7] (*Id.* at 798-802)

Chadwick King ("King"), one of the named inventors on the patents-in-suit, testified that the screening process used in the patent allowed plaintiffs to "identify . . . antibodies that are highly active, have a function of interest, but also have sequence diversity." Sequence diversity helps ensure that there are "enough molecules [so] that one of them can potentially make it through the later stage steps of drug development . . . [and] testing." He opined that the panel of thirty antibodies "had nice sequence diversity" and "cover[ed] multiple epitopes." He concluded that "comparisons of [the] antibody sequences to the germline consensus region" resulted in "good diversity in germline usage." (D.I. 343 at 744-746)

According to Dr. Petsko, 21B12 and 31H4 are sufficiently representative of the asserted claims, as they provide "all the information" needed "to define the part of PCSK9 where the antibodies need to bind in order to block." (D.I. 344 at 806-807, 811) He described generally how an antibody comes together with PCSK9 and that there are different types of chemical interactions possible with an amino acid (for example D238).

[7] Dr. Siegel answered a short series of questions regarding co-binning on cross examination, and conceded that the "epitopes would overlap if [the antibodies] co-bin." (D.I. 343 at 688:14-691:25)

(*Id.* at 808-809) Dr. Petsko agreed that antibodies could have different kinds of chemical interactions with a particular residue, but disagreed with the characterization that such differences result in a significant difference in structure. (*Id.* at 808:24-809:23) Using S153 as an example, Dr. Petsko described "the noncovalent interaction that contributes to the affinity of the antibody for PCSK9." (*Id.* at 815-16) He reasoned that 21B12 binds to S153, R194, R237, D238, D374, T377, and F379 and, therefore, falls within the scope of claims 2, 7, 19, and 29 of the '165 patent and claim 7 of the '741 patent. 31H4 binds to D374 and V380, with a possibility of binding to S381 and, therefore, falls within the scope of claims 15, 19, and 29 of the '165 patent.[8] (*Id.* at 817)

Dr. Petsko explained that using the binning and blocking data, it is "more likely than not that one or more of those [antibodies] are going to make interactions with the residues" of the binding region. He identified which of the co-binned antibodies identified in the patent would "more likely than not" meet the claim limitations of claims 19 and 29 of the '165 patent. (*Id.* at 818-21, 824-25, 827) He opined that although the specification does not disclose "a crystal structure [for] an antibody that binds to I369," the inventors were in possession of such an antibody, because the patent discloses a list of "strong blockers," which would contain antibodies that are likely to bind I369. (*Id.* at 830-32) In other words, the "inventors are in possession of a large number of antibodies and we've described two that cover quite a bit of the [binding region], and we've also indicated the likely presence of antibodies that will interact with even more residues in the [binding region]." (*Id.* at 831-32)

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[8] Dr. Eck disagreed with the detail of Dr. Petsko's analysis (but can "understand where he's coming from") that 21B12 and 31H4 interact with D374. (D.I. 345 at 1120:5-10)

Dr. Petsko testified that, although one could not sit at a desk and write out all the sequences, a scientist would use the information provided to find antibodies that bind to the binding region on PCSK9. (*Id.* at 836:5-837:14) The specification provided sufficient information to conclude that 21B12 and 31H4 are representative. (*Id.* at 818-819) On cross-examination, Dr. Petsko agreed that there could be "many antibodies that recognize the same epitope," and the specification does not provide "the formula" for all of them, but added that "nobody could do that." (*Id.* at 869:14-23) He also conceded that whether an antibody would bind with a particular residue is "not certain at all" from co-binning data. (*Id.* at 880-881, *see also* D.I. 343 at 594:23-595:6, 600:22-601:3) Dr. Jackson concluded that using the X-ray crystallography of 21B12 and 31H4 and the binning data, plaintiffs "knew that the other antibodies were binding in" the binding region. (D.I. 342 at 291-292)

Another of plaintiffs' experts, Dr. Anthony Rees ("Dr. Rees"), also described using binning data to make antibodies and screening them against 21B12 to see if they compete. (D.I. 344 at 917-18) He testified that, from a scientific perspective, making additional antibodies did not require undue experimentation. With "a particular series of steps . . . to follow," it is "routine experimentation with some surprises along the way, but which [a person of ordinary skill] can solve in routine ways." (*Id.* at 920) He evaluated the diversity of the patent's antibodies and concluded that the sequences, which lead to differences in protein sequence and structure, result in "seven different families." He reasoned that this was "quite an extensive diversity." (*Id.* at 923-26) He concluded that a skilled person in the art "would understand that [plaintiffs'] antibodies are representative of the" antibodies of claim 19, based on the disclosure of "detailed three-

Case: 17-1480 Document: 38 Page: 110 Filed: 05/09/2017

dimensional structure" of 21B12 and 31H4, and the twenty-two "other antibodies that are disclosed with respect to their competition or their binning behavior." (*Id.* at 937:17-938:6)

As to a structure-function relationship, Dr. Petsko opined that antibodies can bind through "noncovalent interactions," which "hold them together more often than not." (*Id.* at 791-92) He explained that a "different amino acid sequence might approach a particular residue from a different direction . . . to make a noncovalent interaction with the residue," but this does not affect the structure-function relationship. (*Id.* at 838-40) Dr. Petsko concluded that the specification describes a structure-function relationship by "describing structure characteristics that the antibodies in the genus have in order to carry out the function of binding to PCSK9, blocking the binding of the LDL receptor." More specifically, the "structure function relationship is binding to specific residues on the" binding region. (*Id.* at 783:25-784:19) The specification provides a person of skill in the art the ability to visualize and recognize antibodies falling within the claims based on crystal structures and binning experiments. (*Id.* at 836:22-837:23)

Dr. Rees opined that when an antibody binds to PCSK9, it takes on a unique structure and precisely fits together. So "all the antibodies . . . that bind to this region must share structural features . . . that allow them to get the shape fitting that is required." (*Id.* at 908:10-24, 902:22-903:14, 905:23-906:10) For example, two different amino acid sequences, which bind to the antigen region from influenza may have a different structure, but still share the structural feature of binding to the region. (*Id.* at 910:13-911:18) The "antibodies that fall within the scope of the claims have common structural features." These structural features lead "to the functions of binding and blocking" in order to block the binding of PCSK9 to its LDL receptor. "[T]he consequence of that is there must be a correlation between structure and function." (*Id.* at 912:8-22) On cross-examination, Dr. Rees agreed that the amino acid sequences defined the antibody and the detailed interactions of the amino acids lead to the folded structure. (*Id.* at 986:9-24)

As to the well characterized antigen test, Dr. Petsko testified that he used the term antigen to describe the binding region (part of PCSK9) and that the binding region could be considered a "newly characterized antibody." Dr. Petsko explained how to design more antibodies from the disclosures in the patent – by using 21B12 as a reference, performing binning experiments, testing to see whether the antibodies block the binding to the LDL receptor, and then using developed techniques to screen the antibodies. (*Id.* at 834:17-836:4, 871:10-20; *see also* 915:13-922:24, 937:11-16)

As to enablement, Dr. Rees testified that the state of antibody and engineering sciences is "mature and well established," with well-known methods for creating antibodies, such as those described in the specification. In his opinion, the scope of the claims "is pretty narrow," as they describe "antibodies that bind to a rather small region on the surface of PCSK9." He opined that the specification is a "comprehensive roadmap to how to make . . . [the] antibodies." (*Id.* at 940-41; *see also* D.I. 342 at 401:23-402:7, 417:10-21) He explained that a researcher does not use the binding region to make the antibodies, but the specification teaches "how to analyze for antibodies that bind to" it. (D.I. 344 at 942) Dr. Rees explained that other types of antibodies are well known, including mouse monoclonal antibodies, rat antibodies, and camel antibodies. Moreover, those types of antibodies, as well as fragments, may be made using the information in the specification and routine methods known in the art. (*Id.* at 942-43) On cross-examination, Dr. Rees agreed that the examples of the specification did not describe mouse or camel antibodies. (*Id.* at 981:21-982:12) As to the degree of blocking, Dr. Petsko opined that if an antibody bound to one of the residues, it would be likely that "the big molecule" (with a "pretty big footprint") would cause some blocking. Moreover, the patent disclosed certain "low blocking" antibodies. (*Id.* at 840:5-25) Dr. Petsko agreed that a small amount of blocking would suffice to meet the requirements of certain of the asserted claims. (*Id.* at 870:11-24)

**D. Analysis**

The jury was asked to consider whether defendants presented clear and convincing evidence that the asserted claims of the patents-in-suit lacked written description and enablement. The court instructed the jury that the specification could disclose either "a representative number [of] species falling within the scope of the claimed invention," or "structural features common to the members of the genus, so that a person of ordinary skill in the art can 'visualize or recognize' the members of the claimed invention." The jury was also instructed that "[i]n the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if" the creation of such "antibodies against such an antigen was conventional or routine." (D.I. 299 at 24-25)

The parties and their experts largely agreed on what the specification discloses – a screening process used to select 384 antibodies, which blocked PCSK9 "well" for further testing; a certain subset of antibodies that blocked PCSK9 at over 90%; two antibodies (21B12 and 31H4), which underwent X-ray crystallography analysis; a binding region on PCSK9 of fifteen residues that is the target of such antibodies. The parties' experts also agreed that the art discloses the research techniques necessary to perform antibody development and screening.

The parties' experts analyzed the specification's disclosures and formulated conclusions. Defendants' experts focused on the "middle" portion of the binding region and concluded that insufficient data and examples were disclosed in the specification. Plaintiffs' experts argued the opposite, that is, the examples and disclosures in the patent sufficiently described two antibodies which bind to a large portion of the binding region. An antibody that would bind to the part of the binding region that is not specifically bound by 21B12 and 31H4 is logically within reach using the disclosures of the specification (including the blocking and binning data).

The jury is the finder of fact and is tasked with weighing the evidence and credibility of the witnesses. The parties' experts provided the jury with competing testimony on the interpretation of the data available in the specification. The jury concluded that the asserted claims were not invalid for lack of written description or enablement. Defendants' post-trial arguments essentially ask the court to reevaluate the experts' testimony and reach the opposite conclusion. For example, defendants argue that the two antibodies (21B12 and 31H4) are "plainly insufficient" to represent the genus, and the twenty-two other antibodies that "bin" with 21B12 and 31H4 are not value added as "binning does not allow a person of ordinary skill in the art to determine with any certainty what amino acid an antibody binds to." According to defendants, their experts testified that "nothing disclosed in the [specification] allowed one to visualize or

Case: 17-1480 Document: 91 Page: 114 Filed: 05/29/2017

recognize the structures of the claimed antibodies and to distinguish the claimed antibodies from others." According to defendants, plaintiffs' experts "gave purely conclusory testimony" that the specifications did allow such visualization or recognition. (D.I. 367 at 7, 15)

On the record at bar, plaintiffs' experts provided more than conclusory testimony in order to explain their respective conclusions to the jury. The jury credited such testimony over that of defendants' experts. The court declines to re-weigh the evidence or the credibility of the experts. Viewing the record in the light most favorable to plaintiffs, substantial evidence supports the jury's verdict.[9, 10] For these reasons, defendants' renewed motion for JMOL is denied.

In the alternative, defendants requested a new trial should the court deny the renewed motion for JMOL on written description and enablement. Defendants' request is premised on the same arguments as its renewed motion for JMOL. Defendants again ask the court to "substitute its own judgment of the facts and the credibility of the witnesses," and reach the opposite conclusion as the jury. For the reasons discussed

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[9] Defendants argue that *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), requires a finding that the disclosure is insufficient to meet the representative species test. However, the procedural posture of that case, as well as the facts, are different. Reviewing the district court's findings following a bench trial, the Federal Circuit held that the written description requirement was not met. It reasoned in part that the specification disclosed "only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin." *Id.* at 1567.

[10] The jury's verdict is supported by the evidence on the "representative number of species" or "common structural features" tests, therefore, whether the jury credited the evidence on the "well-characterized antigen" test is not dispositive.

Case: 17-1480 Document: 105 Page: 115 Filed: 05/09/2017

above, the jury's verdict is not against the clear weight of the evidence, therefore, the court denies defendants' request for a new trial.

## V. RECONSIDERATION

In their motion for a new trial, defendants argue that the erroneous exclusion of post-January 2008 evidence substantially prejudiced their defenses of lack of written description and enablement; the jury was erroneously instructed on the test for written description (with respect to the court's "well-characterized antigen" instruction); and the court's grant of JMOL as to obviousness was based on an erroneous interpretation and misapplication of *Dynamic Drinkware v. National Graphics*, 800 F.3d 1375 (Fed. Cir. 2015). While filed as part of a motion for a new trial, defendants essentially request reconsideration of each of the above issues.

A motion for reconsideration is the "functional equivalent" of a motion to alter or amend judgment under Federal Rule of Civil Procedure 59(e). *See Jones v. Pittsburgh Nat'l Corp.*, 899 F.2d 1350, 1352 (3d Cir. 1990) (citing *Fed. Kemper Ins. Co. v. Rauscher*, 807 F.2d 345, 348 (3d Cir. 1986)). The standard for obtaining relief under Rule 59(e) is difficult to meet. The purpose of a motion for reconsideration is to "correct manifest errors of law or fact or to present newly discovered evidence." *Max's Seafood Cafe ex rel. Lou-Ann, Inc. v. Quinteros*, 176 F.3d 669, 677 (3d Cir. 1999). A court should exercise its discretion to alter or amend its judgment only if the movant demonstrates one of the following: (1) a change in the controlling law; (2) a need to correct a clear error of law or fact or to prevent manifest injustice; or (3) availability of new evidence not available when the judgment was granted. *See id.* A motion for reconsideration is not properly grounded on a request that a court rethink a decision already made and may not be used "as a means to argue new facts or issues that inexcusably were not presented to the court in the matter previously decided." *Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239, 1240 (D. Del. 1990); *see also Glendon Energy Co. v. Borough of Glendon*, 836 F. Supp. 1109, 1122 (E.D. Pa. 1993). It goes without saying, therefore, that a motion under Rule 59(e) that advances the same arguments already thought through and rejected by the court - rightly or wrongly - should be denied. *See, e.g., Lazaridis v. Wehmer*, 591 F.3d 666, 669 (3d Cir. 2010); *Savage v. Bonavitacola*, 2005 WL 730679 (E.D. Pa. Mar. 29, 2005), at *1 (citing *Glendon Energy Co. v. Boroough of Glendon*, 836 F. Supp. 1109, 1122 (E.D. Pa. 1993)); *Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239, 1240 (D. Del. 1990).

As to the exclusion of post-January 2008 evidence, the complexity of the matter mandated that the court draw lines and stick to them. (D.I. 345 at 1076:6-1077:25) The court entertained both argument and briefing on this dispute, and issued written orders in support of its decision. (D.I. 226, 249) As to the inclusion of the "well-characterized antigen" jury instruction (D.I. 299 at 25), again the parties were provided opportunity to present argument and briefing, which the court considered. (D.I. 291; D.I. 344 at 1063:5-1065:21) As to the courts' grant of JMOL on obviousness, the court fully considered defendants' arguments as to the applicability of the *Drinkware* case, both before and during trial. (D.I. 250, 282; D.I. 345 at 1076:21-1077:6, 1089:14-17) While defendants disagree with the court's decisions and request that it rethink them, the court declines to do so. The court did not arrive at any of these decisions lightly; indeed, it considered fulsome arguments and briefing. Defendants' request for reconsideration of these issues is denied, as is the motion for a new trial.

Case: 17-1480 Document: 105 Page: 117 Filed: 05/29/2017

For the foregoing reasons, the court denies defendants' motions for a new trial and judgment as a matter of law on written description and enablement (D.I. 331, 332); and denies as moot plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338). An appropriate order shall issue.

## CERTIFICATE OF SERVICE

I hereby certify that on March 3, 2017, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system. I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

s/Paul D. Clement
Paul D. Clement